Statistical Analysis Plan

Sponsor	*Sensorion*
Protocol Title:	*A multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 2 dose regimens of orally administered SENS-111 (100 mg and 200 mg) given during 4 days in patients suffering from Acute Unilateral Vestibulopathy*
Protocol Number:	*SENS 111-201/ NCT03110458*
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Approvals

Role	Signatures	Date (dd-Mmm-yyyy)
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Document History

Reasons for Amendment 1

Updated to clarify some minor ambiguities and inconsistencies and incorporate some decisions made during the study about the analysis populations and the AUC calculation. Typos and updates to the TLF shells are not included in this summary.

Summary of Amended Sections (Amendment 1)

Section 2.2.3 Pharmacokinetic/Pharmacodynamic Variable(s)

Added text: In cases where PK sample cannot be taken at H12 or H24, it is also acceptable to take a PK sample before the 4th intake (H48).

Section 3 Overall Study Design and Plan

Text formerly read: Patients will be included if they are presenting with an acute peripheral vertigo lasting more than 6 hours and less than 3 days, diagnosed as an AUV, and the intensity is at least 60 mm on a 100 mm VAS measured in standing position feet together.

Now reads: Patients will be included if they are presenting with an acute peripheral vertigo lasting more than 6 hours and less than 3 days, diagnosed as an AUV, and the intensity of the vertigo is at least 60 mm on a 100 mm VAS measured in standing position feet together.

Section 3 Overall Study Design and Plan

Text formerly read: Approximately 12 hours after the first study drug intake, patients will be assessed for vital signs and a blood sample will be taken for PK evaluation just before the second dose regimen is given.

Patients will be asked to complete a vertigo VAS for vertigo intensity and nausea intensity twice daily in the morning between 10:00 am and 12:00 pm in the evening after dinner until the end of the study on a specific electronic device, and to record their ability to walk without support. The worst intensity of the spontaneous vertigo over the past 2 hours will be recorded as well as the intensity of the vertigo during standing position.

Twenty-four hours after the first study drug intake, patients will be tested with VOG to measure the severity of their spontaneous nystagmus and a blood sample will be taken for PK just before the study drug intake. Patients will continue to be monitored for vertigo, nausea and vomiting,

vital signs (both supine and standing), ability to unassisted walk, and imbalance assessment (Romberg tests) until discharge from the hospital when a full efficacy assessment will be performed. It will include assessment of the quality of life, and VOG. The same assessments will be performed at the following visit on day 5 and at the end of the study on day 28.

Now reads: Approximately 12 hours after the first study drug intake, patients will be assessed for vital signs and a blood sample will be taken for PK evaluation just before the second dose regimen is given. In cases where PK sample cannot be taken at H12 or H24, it is also acceptable to take a PK sample before the 4th intake (H48).

Patients will be asked to complete a vertigo VAS for vertigo intensity and nausea intensity twice daily in the morning between 10:00 am and 12:00 pm in the evening after dinner until the end of the study on a specific electronic device, and to record their ability to walk without support. The worst intensity of the spontaneous vertigo over the past 2 hours will be recorded as well as the intensity of the vertigo during standing position.

Twenty-four hours after the first study drug intake, patients will be tested with VOG to measure the severity of their spontaneous nystagmus and a blood sample will be taken for PK just before the study drug intake. Patients will continue to be monitored for vertigo, nausea and vomiting, vital signs (both supine and standing), ability to unassisted walk, and imbalance assessment (Romberg tests) until discharge from the hospital when a full efficacy assessment will be performed. It will include assessment of the quality of life, and VOG. The same assessments will be performed at the following visit on day 5 and at the end of the study on day 28. Only the assessments planned during the visits are mandatory. The additional assessments planned during the hospitalization period (i.e. Romberg test twice a day and VNG once a day) are considered optional. In case some of these assessments cannot be performed (for example during the week-end), this should not prevent from including a patient.

Section 3.5 Method of Assigning Subjects to Treatment Groups

Text formerly read: A total of 105 eligible patients will be randomized in a 1:1:1 ratio to one of the 3 treatment groups, stratified by duration of vertigo before being treated (≤ 24 hours, > 24 hours).

Now reads: A total of 105 eligible patients will be randomized in a 1:1:1 ratio to one of the 3 treatment groups, stratified by duration of vertigo before being treated (≤ 24 hours, > 24 hours), as determined at the time of randomization.

Section 4.1 Introduction

Added text: The number of missing values will be calculated as difference of the total number of subjects in the study population for the treatment group minus the number of non-missing values.

Section 4.2 Interim Analysis and Data Monitoring

Text formerly read: The DMC meetings will be held:

- (first meeting) after 30 patients have completed the study
- thereafter, every 35 patients have completed the study or annualy (whichever comes first)

Now reads: The DMC meetings will be held:

- (first meeting) after 30 patients have completed the study
- thereafter, when a further 35 patients (approximately) have completed the study or annualy (whichever comes first)

Section 5 Analysis Populations

Text formerly read: **Enrolled Population (Enrolled):** The Enrolled Population includes all screened, consented, and eligibility validated subjects. This population will be used for disposition and major protocol deviations only.

Now reads: **Screened Population (Screened):** The Screened Population includes all screened and consented subjects. This population will be used for disposition only.

Section 5 Analysis Populations

Text formerly read: **Modified Intention-To-Treat Population (mITT):** The mITT population includes all patients of the ITT population with a baseline standing VI-VAS ≥ 60 mm and with at least one study drug intake.

Now reads: **Modified Intention-To-Treat Population (mITT):** The mITT population includes all patients of the ITT population with a unilateral AUV (diagnosed before or after randomization), a baseline standing VI-VAS ≥ 60 mm and with at least one study drug intake.

Section 5 Analysis Populations

Text formerly read: **Per-Protocol Population (PP):** The PP population includes all patients of the ITT population without a major protocol deviation.

Now reads: **Per-Protocol Population (PP):** The PP population includes all patients of the mITT population with the primary efficacy endpoint (AUC for the

standing VI-VAS) available and without a protocol deviation likely to impact the primary efficacy endpoint.

Section 5 Analysis Populations

Added text: Subjects to be included in the PP Population will be determined by the Sponsor prior to the unblinding of the study. A subject with a protocol deviation who is classified as 'major' per the Protocol Deviation Guidance Plan will be excluded from the PP Population only if the protocol deviation may directly impact the primary efficacy endpoint. Subjects with a major protocol deviation may be excluded from the PP Population if any of the following are met:

- Failure to meet inclusion/exclusion criteria that may impact the primary efficacy endpoint
- Intake of any interfering concomitant medication
- Randomization error

Section 6.1.1 Baseline

Text formerly read: For all efficacy endpoints, the last non-missing observation recorded prior to randomization or during the same day of randomization will be used as the baseline observation for all calculations.

Now reads: For the VAS endpoints, the baseline observation is the first observation recorded in the ePRO on the day of the randomization or otherwise the last observation before the day of the randomization.

For the Romberg score and sub scores, the Average and Peak Slow phase velocity, the baseline observation is the observation recorded in the eCRF at Visit 2 hour 0 provided that this visit is before or the same day as the randomization.

For the DHI score and sub scores, the baseline observation is the observation recorded in the ePRO on the day of eCRF Visit 2 provided that this visit is before or the same day as the randomization.

Section 6.1.6.2 Area under the Curve

Text formerly read: The AUC calculation includes the 4 days of treatment, from baseline to 96±6 hours. All assessments within baseline and baseline + 102 hours will be included in the calculation.
The interval between baseline and the first post-baseline assessment will be included in the AUC calculation. If some or all of the 8 post-baseline assessments are recorded after treatment discontinuation then they will be included in the AUC calculation. The 9th post-baseline assessment will be

included in the AUC calculation when recorded not later than 102 hours post baseline.

Now reads: The AUC calculation includes the 4 days of treatment, from baseline to 96±6 hours. All assessments within baseline and baseline + 102 hours will be included in the calculation. The AUC will not be calculated if no baseline value is available or if no VAS assessment is available between 18 (12+6) hours and 102 (96+6) hours from baseline for reason not linked to severe vertigo.
The interval between baseline and the first post-baseline assessment will be included in the AUC calculation.

Section 6.1.6.3 Romberg Total Score and Subscores

Text formerly read: The average scores of the Romberg test in the morning and evening will be used when two assessments are available.

Now reads: The average scores of the Romberg test in the morning and evening will be used when two assessments are available for the same visit.

Section 6.1.6.4 DHI total score and subscores

Text formerly read: F1, F3, F5, F6, F7, F12, F16, F19, F24

Now reads: F3, F5, F6, F7, F12, F16, F19, F24

Section 6.1.6.5 VADL total score and subscores

Text formerly read: NEED SPECIAL ASSISTANCE = 8

Now reads: NEED PHYSICAL ASSISTANCE = 8

Section 7.1 Disposition of Patients and Withdrawals

Text formerly read: The total number of subjects for each of the following categories will be presented for the enrolled population:

- Enrolled Population
- Safety Population
- ITT Population
- mITT Population
- PP Population
- Ancillary Population
- Expose patients (those who take at least 1 dose of study drug)
- Completed patients up to visit 7, Day 28 (±2 days)
- Patients remaining on treatment at each visit

- Patients withdrawn
- Reasons for early study termination

Now reads: The total number of subjects for each of the following categories will be presented for the screened population:

- Screened Population
- Safety Population
- ITT Population
- mITT Population
- PP Population
- Ancillary Population
- Completed patients up to visit 7, Day 28 (±2 days)
- Patients at each visit
- Patients withdrawn
- Reasons for early study termination

Section 7.2. Protocol Violations and Deviations

Text formerly read: Major protocol violations – i.e. those leading to exclusion from the PP population – will be summarized by type of violations, overall and by center for the enrolled population.

Now reads: Major protocol violations – i.e. those leading to exclusion from the PP population – will be summarized by type of violations, overall and by center for the ITT population.

Section 8.1 Primary Efficacy Analysis

Text formerly read: The standing VI-VAS will be summarized using descriptive statistics of absolute values and changes from baseline at each assessment, and of the AUC including the length of the AUC observation period.

Now reads: The standing VI-VAS will be summarized using descriptive statistics of absolute values and changes from baseline at each mapped time point, and of the AUC including the length of the AUC observation period. Each VAS assessment will be mapped to a time point as follows:

Time point (mapped value)	VAS assessment time since baseline (hours)
12 hours	6 (excluded) to 18 (included)
24 hours	18 (excluded) to 30 (included)
36 hours	30 (excluded) to 42 (included)

…	

When more than one VAS assessment fall within the same time window, then only the VAS assessment closest to the middle point will be assigned to the time point. In case of values that are equidistant to the middle point, the latest assessment only will be assigned to the time point. VAS assessment not mapped to time point will not be included in the summary statistics and in the MMRM analysis.

Section 8.1 Primary Efficacy Analysis

Text formerly read: The VI-VAS AUC will be compared between treatment groups within an analysis of covariance model (ANCOVA) with the stratification factor duration of vertigo (≤24 hours, >24 hours before being treated) and the baseline VI-VAS as covariates. The two comparisons to placebo (SENS-111 at 100 mg vs placebo, and SENS-111 at 200 mg vs placebo) will be tested for superiority at 5% one-sided significance level, the corresponding 90% two-sided confidence intervals will be presented.

Now reads: The VI-VAS AUC will be compared between treatment groups within an analysis of covariance model (ANCOVA) with the stratification factor duration of vertigo (≤24 hours, >24 hours before being treated) and the baseline VI-VAS as covariates. The two comparisons to placebo (SENS-111 at 100 mg vs placebo, and SENS-111 at 200 mg vs placebo) will be tested for superiority at 5% one-sided significance level, the corresponding 90% two-sided confidence intervals will be presented. In addition the pool of the two active doses (SENS-111 at 100 mg and SENS-111 at 200 mg) will also be tested for superiority at 5% one-sided significance level, and the corresponding 90% two-sided confidence interval will be presented.

Section 8.1 Primary Efficacy Analysis

Text formerly read: As a complementary analysis in order to get a better insight of the treatment effect over time, the 8 post baseline VI-VAS scores will be analyzed, without replacement of missing values, using a restricted maximum likelihood (REML) based repeated measures approach.

Now reads: As a complementary analysis in order to get a better insight of the treatment effect over time, the 8 post baseline VI-VAS scores at mapped time points (12h, 24h, 36h, 48h, 72h, 84h, 96h) will be analyzed, without replacement of missing values, using a restricted maximum likelihood (REML) based repeated measures approach.

Section 8.1 Primary Efficacy Analysis

Added text: The same MMRM approach will repeated using all mapped time points up to 672 h (D28) included excluding the time points where the available

sample size represents less than 75% of the analysis set. This additional analysis will provide some information on the long-term recovery of the vestibular function.

Section 8.2.4 Peak slow phase velocity at the end of treatment and end of study

Added text: The analysis for the peak slow phase velocity will be repeated for each testing condition: no fixation (30 sec) and fixation (10 sec).

Section 8.3.3 Time to unassisted walking

Text formerly read: Time to unassisted walking from Day 1, i.e. Visit 2 Inclusion H0, in hours will be analyzed using a descriptive time-to-event approach (Kaplan-Meier).'

Now reads: Time to unassisted walking from Day 1, i.e. Visit 2 Inclusion H0, in days will be analyzed using a descriptive time-to-event approach (Kaplan-Meier).

Section 8.3.3 Time to unassisted walking

Added text: A Cox proportional hazard regression model with a categorical variable for the treatment arm as independent variable will also be used to estimate the hazard ratios for the treatment effects (SENS111 100 mg vs placebo, and SENS111 200 mg vs placebo), which will be presented together with two sided 90% confidence intervals, as well as the corresponding P value.

Section 9.5.4 Hospitalization due to AUV

Text formerly read: Hospitalization due to AUV, the type of ward, and the length of hospital stay will be summarized by treatment arm.

Now reads: Hospitalization due to AUV (including participation in the study), the type of ward, and the length of hospital stay will be summarized by treatment arm.

Section 10 Changes from Planned Analysis

Text formerly read: The Enrolled Population, the modified Intention-to-Treat Population and the Ancillary Population are not described in the protocol and they have been added in Section 5.

Now reads: The Screened Population, the modified Intention-to-Treat Population and the Ancillary Population are not described in the protocol and they have been added in Section 5.

Section 10 Changes from Planned Analysis

Added text: The PP Population definiton has been amended. Patients with major protocol deviations are excluded from the PP Population in the protocol, while patients with major protocol deviation likely to impact the primary efficacy endpoint are excluded from the PP Population in this SAP.

Section 13 Tables, Listings, and Figures

The following tables and listings have been added:

- 14.2.1.6 Statistical Analysis of Standing VI-VAS: MMRM (12H to 672H)
- 14.2.2.6 Statistical analysis of Worst VI-VAS: MMRM (12H to 672H)
- 14.2.3.6 Statistical Analysis of Nausea Intensity VAS: MMRM (12H to 672H)
- 16.2.9.8 CT Scan and MRI Scan

Reasons for Amendment 2

Updated to include sensitivity analyses of Standing VI-VAS, Worst VI-VAS, and Nausea Intesity VAS and AUCs. Typos and updates to the TLF shells are not included in this summary.

The amended SAP version 1.2 will be finalized and submitted to file prior to the unblinding for final analysis.

Section 8.1 Primary Efficacy Analysis

Added text: A sensitivity analysis using the date/time of the first dose intake of randomized study drug as the time reference for the AUC calculation will also be performed. In this analysis, the baseline will be defined as the last observation recorded in the ePRO until the time of the first dose intake and the AUC calculation will conducted as defined in section 6.1.6.2 (using all VAS assessments between baseline and baseline + 102 hours). This analysis will be conducted on the mITT and the PP restricted to subjects for whom the baseline standing VI-VAS based on first study drug intake is available and ≥ 60 mm.

Section 8.1 Primary Efficacy Analysis

Added text: The same analysis using baseline and mapped time points both defined with reference to time of first dose intake will be applied on the mITT and

the PP restricted to subjects for whom the baseline standing VI-VAS based on first study drug intake is available and ≥ 60 mm.

Section 8.1 Primary Efficacy Analysis

Text formerly read: The same MMRM approach will be repeated using all mapped time points up to 672 h (D28) included excluding the time points where the available sample size represents less than 75% of the analysis set.

Now reads: The same MMRM approach will be repeated using all mapped time points up to 672 h (D28) included.

Section 13 Tables, Listings, and Figures

The following tables and listings have been added:

- 14.2.1.7 Sensitivity Analysis of AUC for Standing VI-VAS: ANCOVA
- 14.2.1.8 Sensitivity Analysis of Standing VI-VAS: MMRM (12H to 96H)
- 14.2.2.7 Sensitivity Analysis of AUC for Worst VI-VAS: ANCOVA
- 14.2.2.8 Sensitivity Analysis of Worst VI-VAS: MMRM (12H to 96H)
- 14.2.3.7 Sensitivity Analysis of AUC for Nausea Intensity VAS: ANCOVA
- 14.2.3.8 Sensitivity Analysis of Nausea Intensity VAS: MMRM (12H to 96H)

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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Sensorion protocol number SENS 111-201 (A multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 2 dose regimens of orally administered SENS-111 (100 mg and 200 mg) given during 4 days in patients suffering from Acute Unilateral Vestibulopathy), dated 05-Nov-2018 version #4.0. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Sensorion's study SENS 111-201.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to assess the efficacy of SENS-111 in Acute Unilateral Vestibulopathy (AUV).

2.1.2. Secondary Objectives

The secondary objectives are:

- To explore the effect of SENS-111 on quality of life
- To determine the optimal dose regimen of SENS-111
- To evaluate safety and tolerability of SENS-111 in patients with AUV
- To evaluate the effect of SENS-111 on long-term recovery of vestibular function
- To characterize the plasma exposure to SENS-111 in patients with AUV
- To preliminary evaluate the health economics of SENS-111

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints are adverse events (AEs), laboratory, vital signs, and ECG.

Each AE will be coded to a Preferred Term and associated System Organ Class (SOC) according to an established and validated adverse reaction dictionary (MedDRA, version 20.0) before the randomized treatment code is broken.

The AE endpoints are number of patients experiencing:

- at least 1 event
- an event under each recorded Preferred Term
- an event under each recorded SOC

These endpoints apply to all AEs, regardless of relationship of the event to the study drug.

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the vertigo intensity measured by the area under the curve (AUC) of the Vertigo Intensity Visual Analogue Scale (VI-VAS) in standing position over the 4 treatment days (8 post-baseline assessments).

2.2.2.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints deal with the comparison between treatment groups of:

1. Worst spontaneous vertigo intensity measured by the AUC of the worst VI-VAS over the 4 treatment days (8 post baseline assessments)
2. Change from baseline of the total score of the Romberg tests at the end of the treatment (D5) and at the end of study (D28)
3. Change from baseline of the peak slow phase velocity (SPV) of the peripheral vestibular spontaneous nystagmus, measured by oculography in darkness at the end of the treatment (D5) and end of study (D28)
4. Nausea severity measured by the AUC of the Nausea Intensity Visual Analogue Scale (NI-VAS) over the 4 treatment days (8 post baseline assessments)
5. Change from baseline of the functional disability at the end of study (D28) assessed by the Dizziness Handicap Inventory (DHI) functional subscale score
6. The functional disability at the end of study (D28) assessed the Vestibular Disorders Activities of Daily Living Scale (VADL)

2.2.2.3. Exploratory Efficacy Endpoint(s)

The exploratory efficacy endpoints of this study include the following:

1. Vertigo Intensity in standing position at the end of the study (D28) assessed by the VI-VAS
2. Worst spontaneous vertigo at the end of the study (D28) assessed by the VI-VAS
3. Time to unassisted walk assessed by a specific question
4. Health economic evaluation assessed with the Work Productivity and Activity Impairment (WPAI-SHP) questionnaire at the end of study.

2.2.3. Pharmacokinetic/Pharmacodynamic Variable(s)

Serum samples are collected for pharmacokinetic (PK) analysis at 3 time points: H12, H24, and at end of treatment visit (D5). In cases where PK sample cannot be taken at H12 or H24, it is also acceptable to take a PK sample before the 4th intake (H48*).* Plasma concentration of SENS-111 will be used as the parameter to describe the plasma exposure to SENS-111.

No pharmacodynamic (PD) variables are being investigated in this study.

2.2.4. Ancillary Endpoints

Additional tests will be performed at baseline and at the end of the study in sites participating in the ancillary study:

- Video-head impulse test (vHIT) which provides a quick and objective measure of the vestibular ocular reflex (VOR) in response to head movements
- Caloric test which provides two parameters: total response (TR) and relative vestibular reduction (RVR)

3. Overall Study Design and Plan

The study is a double-blind, randomized, 3 parallel-group placebo-controlled, international study in patients with acute unilateral vestibulopathy.

This study will be a multicenter international study conducted in about 38 sites in Europe, Israel, US, and South Korea. Each patient's participation in the study will be 28 days: 4 days of double blind treatment, and a 24-day follow-up with no investigational product.

The study will assess the efficacy and safety of orally administered SENS-111 in patients with acute unilateral vestibulopathy.

Patients will be included if they are presenting with an acute peripheral vertigo lasting more than 6 hours and less than 3 days, diagnosed as an AUV, and the intensity of the vertigo is at least 60 mm on a 100 mm VAS measured in standing position feet together.

It is planned to enroll 105 patients into 3 arms in a 1:1:1 ratio:

- 35 patients receiving SENS-111 200 mg daily for 4 days
- 35 patients receiving SENS-111 100 mg daily for 4 days
- 35 patients receiving matching placebo

This study includes a screening/inclusion phase, a treatment phase, and a follow-up phase. The screening and inclusion are to be done no more than 12 hours apart. As soon as eligibility of the patient is confirmed, the investigator will dispense the study drug to the subject; the study drug is to be taken immediately after all baseline assessment are performed.

The screening evaluation includes: vital signs, a complete oto-neurological examination, a nausea and vertigo evaluation that will confirm the diagnosis and the absence of exclusion criteria for past medical history, concomitant treatments, laboratory tests, or other concomitant diseases. Specific attention will be paid to exclude any patient with a stroke in the last 3 months (a negative past MRI is needed for inclusion of patients with possible stroke of the brainstem or cerebellum).

Following this screening phase, eligible patients will undergo a nystagmus evaluation with a videooculography (VOG), and either a head impulse test or caloric test or both to confirm the diagnosis. They will complete vertigo evaluations with VAS scores and questionnaires, assessment of imbalance (Romberg tests), nausea and vomiting scales just before the first intake of the investigational drug at the investigational site. Patients will be requested to stay under medical supervision for at least 6 hours after the first study drug intake for safety. Approximately 12 hours after the first study drug intake, patients will be assessed for vital signs and a blood sample will be taken for PK evaluation just before the second dose regimen is given. In cases where PK sample cannot be taken at H12 or H24, it is also acceptable to take a PK sample before the 4th intake (H48).

Patients will be asked to complete a vertigo VAS for vertigo intensity and nausea intensity twice daily in the morning between 10:00 am and 12:00 pm in the evening after dinner until the end of the study on a specific electronic device, and to record their ability to walk without support. The worst intensity of the spontaneous vertigo over the past 2 hours will be recorded as well as the intensity of the vertigo during standing position.

Twenty-four hours after the first study drug intake, patients will be tested with VOG to measure the severity of their spontaneous nystagmus and a blood sample will be taken for PK just before the study drug intake. Patients will continue to be monitored for vertigo, nausea and vomiting, vital signs (both supine and standing), ability to unassisted walk, and imbalance assessment (Romberg tests) until discharge from the hospital when a full efficacy assessment will be performed. It will include assessment of the quality of life, and VOG. The same assessments will be performed at the following visit on day 5 and at the end of the study on day 28. Only the assessments planned during the visits are mandatory. The additional assessments planned during the hospitalization period (i.e. Romberg test twice a day and VNG once a day) are considered optional. In case some of these assessments cannot be performed (for example during the week-end), this should not prevent from including a patient.

Patients will be followed for AEs throughout the study. Inquiry about potential AEs will be done at every on-site visit and on day 14 when a phone call will be given.

Safety parameters will include routine blood tests (complete blood count, chemistry, liver function tests and lipid profile), pregnancy tests (if applicable), cardiac evaluation by ECG, physical exams and vital signs (with orthostatic blood pressure).

The WPAI-SHP questionnaire will be requested at the end of study visit (D28).

Additional tests will be conducted at some specific sites participating in an ancillary study:

- video Head Impulse Test at the end of treatment visit (D5) and end of study visit (D28)
- caloric test at the baseline and end of study visit (D28)

For full details of the study design, please refer to the protocol.

3.1. Overall Design

3.2. Sample Size and Power

The sample size calculation is based on the AUC of the VI-VAS from baseline included to second measurement of Day 4 included.

The assumptions are the followings:

- Each comparison to placebo performed at 5% one-sided-significance level
- Power of each comparison to placebo set to 75%
- Randomization ratio 1:1:1
- Intra-group standard deviation of 71 mm/day
- Difference to placebo of 40 mm/day (i.e. 20% of an average AUC of 200 mm/day on placebo)

3.3. Study Population

Men and women aged 18-75 years, suffering from Acute Unilateral Vestibulopathy.

3.4. Treatments Administered

Orally disintegrating tablets (ODT) will be given once daily for 4 days:

- SENS-111 200 mg: 100 mg ODT + 100 mg ODT
- SENS-111 100 mg: 100 mg ODT + placebo ODT
- Matching placebo: placebo ODT + placebo ODT

The orally disintegrating placebo tablets match SENS-111 (100 mg) tablets, and are identical in appearance. An additional dose (respectively 200 mg, 100 mg and placebo) will be administered to the patients approximately 12 hours after the first intake. The corresponding total dose for the 3 arms will be 1000 mg, 500 mg, 0 mg, respectively.

3.5. Method of Assigning Subjects to Treatment Groups

The randomization will be managed centrally using an interactive web system response (IWRS).

A total of 105 eligible patients will be randomized in a 1:1:1 ratio to one of the 3 treatment groups, stratified by duration of vertigo before being treated (≤ 24 hours, > 24 hours), as determined at the time of randomization.

A patient will be considered randomized when the IWRS has given the treatment number to be allocated.

All randomized subjects (Day 1) will receive either SENS 100 mg x 2 ODT, or SENS 100 mg x 1 ODT and Placebo x 1 ODT, or Placebo x 2 ODT at the study site according to the IWRS allocation.

- The treatment will be given once daily.
- The first dose (2 ODT) will be given at the site.
- An additional dose (2 ODT) will be given approximately 12 hours after the first dose (not less than 9 hours and no more than 15 hours after the first dose).

3.6. Blinding and Unblinding

The orally disintegrating placebo tablets match SENS-111 (100 mg) tablets, and are identical.

Pharmacokinetic parameters that could potentially unblind the study team will not be disclosed during the conduct of the study.

Investigators will have no access to the randomization code except under the special circumstances. In case of an emergency, when knowledge of the randomization status is deemed necessary for the medical care of the patient, the randomization code can be unblinded for a specific patient.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 1 Schedule of Events

		Double-blind Treatment				Follow-up	
Visit	**V1 Screening**	**V2 Inclusion**	**V3**	**V4 End of Hospitalization Visit 4·4**	**V5 End of Treatment Visit**	**V6 (Phone Call)**	**V7 End of study visit**
	H-6 (± 6)	**D1 (H0)**	**D2(H24±3)**	**D3 (-1, +25)**	**D5 (-1,+2)**	**D14 (±2)**	**D28 (±2)**
Informed Consent/Demography/Medical History	X						
Inclusion/Exclusion Criteria	X	X					
Physical Examination	X				X		X
Vital signs (BP standing and supine, HR), Temperature	X	X	X	X	X		X
ECG	X				X		X
Neuro Otologic examination	X				X		X
Prior Medication History	X	X					
Routine serum Hematology and Chemistry	X				X		
Pregnancy test/Pregnancy status [5]	X				X		X
Concomitant medications		X	X	X	X	X	X
Randomization		X					
Efficacy							
Standing vertigo intensity [11]	←----	----------	--------	----------	----------	----------	---------→
Worst vertigo intensity (VAS) [1]		←----------	--------	----------	----------	----------	---------→
Nausea Intensity (VAS)1	←----	----------	--------	----------	----------	----------	---------→
Walking assessment [1]		←----------	--------	----------	----------	----------	---------→

		Double-blind Treatment				Follow-up	
Visit	**V1 Screening**	**V2 Inclusion**	**V3**	**V4 End of Hospitalization Visit 4·4**	**V5 End of Treatment Visit**	**V6 (Phone Call)**	**V7 End of study visit**
	H-6 (± 6)	**D1 (H0)**	**D2(H24±3)**	**D3 (-1, +25)**	**D5 (-1,+2)**	**D14 (±2)**	**D28 (±2)**
Disability Handicap Inventory (DHI)		**X**					**X**
VADL							**X**
Romberg tests 7		**X**	**X**	**X**	**X**		**X**
VideoOculography (spontaneous nystagmus) 6		**X**	**X**	**X**	**X**		**X**
Hospitalization (Yes/No)		**X**	**X**	**X**	**X**	**X**	**X**
Health Economic questionnaire							**X**
Ancillary Efficacy Study							
Video-head impulse test (function of the vestibulo-ocular reflex		**X9**			**X**		**X10**
Caloric test [12] (optional)		**X9**					**X10**
Treatment							
Study Drug Intake [2, 3]		**X←----**	**--------**	**----------→**			
Compliance			**X**	**X**	**X**		
Safety							
Adverse events	←-----	----------	--------	----------	----------	----------	----------→
Pharmacokinetics [8]		**X**	**X**		**X**		

1. VAS and walking assessment will be completed at the inclusion visit prior to the first study drug intake and then twice daily in the morning at 10 am and in the evening just after dinner from the inclusion visit to end of study visit.

2. The first dose should be taken at the site (H0), immediately after all baseline assessments are performed and the patient is randomized in the IWRS. The second dose will be given 12 hours after (±3 h). The following doses will be taken on Day 2 (H24±3h), Day 3 (H48±3h) and Day 4 (H72±3h).
3. Patients will receive the remaining tablets to be taken home if he/she is discharged from the hospital prior to the last scheduled intake: Total intake of 2 tablets x 5.
   The last dose will be given either in the morning or evening of D4 according to the time of first intake.
4. If the patient remains hospitalized after Day 28, the end of hospitalization visit will not be completed. The end of hospitalization visit has to be completed if it does not occur at the same time as another scheduled visit (D5: end of treatment visit or D28, the end of study visit The reason for not performing the end of hospitalization visit will be filled in the e CRF.
5. Pregnancy tests will be either urine or blood test (If the urine test is positive a blood test will be done for confirmation).
6. Video oculography will be performed at the inclusion visit prior to the first study drug intake, and at all subsequent onsite visits. In addition, when possible Video oculography will be performed daily until the end of hospitalization.
7. The Romberg tests will be performed at the inclusion visit prior to the first study drug intake, and at all subsequent onsite visits. In addition, when possible Romberg test will be performed twice daily in the morning and evening while hospitalized.
8. 12 hours (± 3) after the first study drug intake, vital signs will be measured and a blood sample will be taken for PK **just before the second study drug intake**. Two other blood samples will be taken. One just before the 3rd study drug intake at H24 and one at the end of treatment visit. In cases where PK sample cannot be taken at H12 or H24, it is also acceptable to take a PK sample before the 4th intake (H48).
9. Either HIT or caloric test are needed for confirmation of the diagnosis
10. The caloric test and HIT at the end of study visit are optional and part of an ancillary study
11. The standing vertigo VAS will be completed under condition 1 of the Romberg tests at the site twice daily. At home, it will be performed twice daily in standing position, eyes open, feet together on a firm surface.
12. Caloric test can be performed using either water or air according to the usual practice at the site.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, the number of missing values, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise specified.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment groups, unless otherwise specified.

The number of missing values will be calculated as difference of the total number of subjects in the study population for the treatment group minus the number of non-missing values.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

4.2. Interim Analysis and Data Monitoring

An independent Data Monitoring Committee (DMC) will independently monitor subject safety during the SENS 111-201 study. The primary goal of the DMC is to protect and to promote safety of patients participating in the trial. Other goals are to monitor study integrity, to evaluate the adequacy of data demonstrating safety of treatments independently from the investigational centres and the sponsor and finally to make decision about study continuation based on safety data.

The DMC is an independent multidisciplinary group consisting of at least 2 physicians and a statistician that collectively has experience in the management of patients with vestibulopathies and in the conduct and monitoring of randomized clinical trials. The DMC does not include Sponsor's personnel or personnel from Contract Research Organizations (CRO) appointed by the Sponsor.

The DMC meetings will be held:

- (first meeting) after 30 patients have completed the study
- thereafter, when a further 35 patients (approximately) have completed the study or annualy (whichever comes first)

The DMC will remain blinded for its evaluation, but may request unblinded or partially blinded reports. The unblinded or partially blinded analysis will be performed by an independent statistician other than the author of this plan or the person responsible for the primary analysis of this study and treatment codes will be revealed to that party only.

The DMC is empowered to make recommendations on the SENS-111-201 study based on the results of their reviews. The possible recommendations the DMC can make are to:

- Continue the trial without modification
- Continue the trial with protocol amendments (DMC will provide details of suggested modifications and reasons for the modifications according to the benefit/risk ratio)
- Modify or strengthen safety procedures
- Suspend enrolment and treatment administration in the trial pending further information
- Terminate the trial earlier

The scope of responsibility of the DMC, its membership and its confidentiality, as well as the frequency, content, and format of data review meetings, is described in a separate DMC charter of operations approved by Sensorion and by the DMC members prior to the first review meeting.

No other interim analysis, except DMC analysis, is planned.

5. Analysis Populations

The followings are planned for this study:

- **Screened Population (Screened):** The Screened Population includes all screened and consented subjects. This population will be used for disposition only.
- **Safety Population (SAF):** The Safety Population includes all treated patients according to first treatment actually received. Note that the Safety population may also be referred as Safety Analysis Set.
- **Intention-To-Treat Population (ITT):** The ITT population includes all randomized patients.
- **Modified Intention-To-Treat Population (mITT):** The mITT population includes all patients of the ITT population with a unilateral AUV (diagnosed before or after randomization), a baseline standing VI-VAS $\geq$ 60 mm and with at least one study drug intake.
- **Per-Protocol Population (PP):** The PP population includes all patients of the mITT population with the primary efficacy endpoint (AUC for the standing VI-VAS) available and without a protocol deviation likely to impact the primary efficacy endpoint.
- **Ancillary Population (ANC):** The Ancillary Population includes all patients performing ancillary tests, i.e video-head impulse test and/or caloric test.

The ITT population will be the primary population for efficacy analysis. The PP population will be secondary for the efficacy analysis. The mITT population will be used for a sensitivity

efficacy analysis in a selection of endpoints: standing VI-VAS, worst VI-VAS, and nausea intensity VAS. The SAF will be used for the analyses of safety endpoints.

All efficacy analyses will be conducted according to the randomized treatment assignment by IWRS; all safety analyses will be conducted to the treatment actually received.

Subjects to be included in the PP Population will be determined by the Sponsor prior to the unblinding of the study. A subject with a protocol deviation who is classified as 'major' per the Protocol Deviation Guidance Plan will be excluded from the PP Population only if the protocol deviation may directly impact the primary efficacy endpoint.

Subjects with a major protocol deviation may be excluded from the PP Population if any of the following are met:

- Failure to meet inclusion/exclusion criteria that may impact the primary efficacy endpoint
- Intake of any interfering concomitant medication
- Randomization error

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

For the VAS endpoints, the baseline observation is the first observation recorded in the ePRO on the day of the randomization or otherwise the last observation before the day of the randomization.

For the Romberg score and sub scores, the Average and Peak Slow phase velocity, the baseline observation is the observation recorded in the eCRF at Visit 2 hour 0 provided that this visit is before or the same day as the randomization.

For the DHI score and sub scores, the baseline observation is the observation recorded in the ePRO on the day of eCRF Visit 2 provided that this visit is before or the same day as the randomization.

For all safety endpoints, the last non-missing observation recorded prior to the first drug intake will be used as the baseline observation for all calculations.

6.1.2. Multiple Comparisons

No adjustment will be made for multiple comparisons due to the exploratory nature of the hypothesis testing.

6.1.3. Handling of Dropouts or Missing Data

In general, no data will be imputed.

Missing intermediate measurements of the standing VI-VAS, worst VI-VAS, and NI-VAS won't be replaced in the calculation of the AUC. Since the trapezoid rule will be used to calculate the AUC, linear interpolation of intermediate values or no imputation at all will lead to the same AUC estimation. Missing final measurement(s) (e.g. in case of patient's withdrawal) will be replaced by BOCF (baseline observation carried forward) if the reason for missing data is severe vertigo or by LOCF (last observation carried forward), i.e. absence of improvement, if the reason for missing data is nausea, other or unknown.

A mixed model without replacement of missing values using a restricted maximum likelihood (REML) for repeated measures will be conducted to examine whether or not results are robust to the data imputation.

Any subject who withdraws from the study will be considered as study discontinuation. Subjects who discontinue study should be assessed in accordance with the assessments/tests specified normally for the end of the study visit.

6.1.4. Analysis Visit Windows

As per protocol a window of ±6 hours is allowed for the screening visit, while a window of ±3 is allowed for visit at H12 and H24. For the end of treatment visit, a window of -1 to +2 days is allowed. A window of ±2 days is allowed for the phone call visit and the end of study visit. Statistical analyses will be based on scheduled visit as collected in the eCRF without further realignment.

6.1.5. Pooling of Sites

As there are expected to be relatively few patients per centre, the centre will not be taken into account in the analyses. Therefore the question of pooling of centres does not arise. However, a breakdown by center will be given in summary tables for patients' disposition.

6.1.6. Derived Variables

The following derived and computed variables have been initially identified as important for the analysis of efficacy.

It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create the analysis files. If the SAP is not amended, further derivations related to primary and secondary target variables will be described in the CSR.

6.1.6.1. Treatment-emergent adverse events

Treatment-emergent adverse events (TEAE) are defined as events occurring after the first dose intake of randomized study drug, and up to and including 10 days after the last dose of study drug. Additionally, events present before the first dose of randomized study drug, but worsening under treatment are considered as TEAE. Events with treatment status unclear because the onset date and/or the dates of first/last study drug intake are missing or incomplete will be considered as TEAEs.

If the start date of an AE are partially or completely missing, the AE will be assumed to be treatment-emergent if it cannot be definitely shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach). Missing dates will not be replaced.

The following are used for guidance for programmers.

- If the start date of the AE is complete, the AE will be excluded from treatment-emergent AEs if the start day is before day of first treatment or the start day is after end day of the treatment-emergent period.
- If the day is missing but the start month is complete, an AE will only be excluded from treatment emergent AEs if the start month is before month of first treatment or the start month is after end month of treatment-emergent period or if the stop date is before the start of first treatment.
- If the start day and months are missing but the start year is complete, an AE will only be excluded from treatment-emergent AEs if the start year is before year of first treatment or if the start year is after end year of treatment-emergent period or if the stop date is before the start of first treatment.

If the start date is completely missing, an AE will not be excluded from treatment-emergent AEs unless the stop date is before the start of first treatment.

6.1.6.2. Area under the curve

The baseline assessment and the first 8 first post-baseline assessments will be included in the calculation of the AUC.

The AUC calculation includes the 4 days of treatment, from baseline to 96±6 hours. All assessments within baseline and baseline + 102 hours will be included in the calculation. The AUC will not be calculated if no baseline value is available or if no VAS assessment is available between 18 (12+6) hours and 102 (96+6) hours from baseline for reason not linked to severe vertigo.

The interval between baseline and the first post-baseline assessment will be included in the AUC calculation. Skipped assessments do not extend the time interval used. Missing intermediate measurements will not be replaced in the calculation of the AUC. Missing final measurements will be replaced as described in Section 6.1.3 with time of assessment equal to 96 hours.

The AUC for the VAS will be calculated using the trapezoidal rule, which is based on the formula to find the area of a trapezoid: take the sum of its basis, multiply the sum by the height of the trapezoid, and the divide the results by 2.

Therefore, the VAS-AUC in mm/day will be:

$$\mathrm{AUC} = \frac{1}{2}\sum_{j=0}^{J-1}(\mathrm{VAS}_j + \mathrm{VAS}_{j+1})(t_{j+1} - t_j)$$

where:

- the VAS assessments $\mathrm{VAS}_0, \mathrm{VAS}_1, \ldots, \mathrm{VAS}_j, \ldots, \mathrm{VAS}_J$ are made at times $t_0, t_1, \ldots, t_j, \ldots, t_J$
- t_0 is the time at baseline

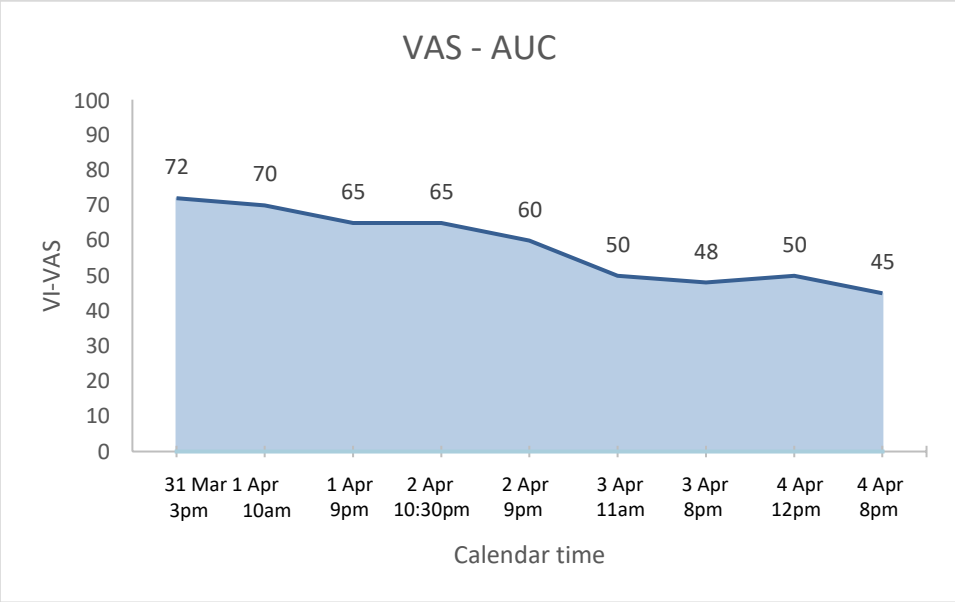
- VAS_0 is the VAS assessment at baseline
- t_J is the latest time with $t_J - t_0 \leq 102$ hours

An example of the AUC estimation is illustrated in Table 2 and Figure 1.

Table 2 AUC estimation

j	VAS score (VAS_j)	Date and time (t_j)	Sum of basis of the trapezoid ($VAS_j + VAS_{j+1}$)	Height of trapezoid in days ($t_{j+1}-t_j$)	Area of the trapezoid (mm/day) $0.5 (VAS_j + VAS_{j+1}) (t_{j+1}-t_j)$
0	72	31 March 2017, 3:00pm	142	0.792	56.208
1	70	1 April 2017, 10:00am	135	0.458	30.938
2	65	1 April 2017, 9:00pm	130	0.563	36.563
3	65	2 April 2017, 10:30am	125	0.438	27.344
4	60	2 April 2017, 9:00pm	110	0.583	32.083
5	50	3 April 2017, 11:00am	98	0.375	18.375
6	48	3 April 2017, 8:00pm	98	0.667	32.667
7	50	4 April 2017, noon	95	0.347	15.833
8	45	4 April 2017, 8:00pm	-	-	-
				Total	250.010

Figure 1 AUC estimation



This method will apply to VI-VAS measurements for the standing position and the worst vertigo intensity, and NI-VAS as well.

The estimation of the AUC is complicated by the fact that this parameter is time-dependent; its value depends on the length of the observation period: t_8-t_0. Specific attention will be paid to check that the variability of the observation period between treatment arms does not affect the calculation of the AUC.

6.1.6.3. Romberg total score and subscores

The Romberg test assess the patient's ability to stand unassisted under 6 successive test conditions of increasing difficulty:

Condition	Description	Score
1	Standing on the floor, feet together (or at a distance for them to be steady) with the eyes open looking straight ahead	sc_1
2	Standing on the floor, feet together (or at a distance for them to be steady) with the eyes closed	sc_2
3	Standing on a foam pad, feet together (or at a distance for them to be steady) with the eyes open looking straight ahead	sc_3
4	Standing on a foam pad, feet together (or at a distance for them to be steady) with the eyes closed	sc_4
5	Standing, on a foam pad, feet heel to the toes with the eyes open looking straight ahead (dominant foot directly in front of the non-dominant foot in tandem)	sc_5
6	Standing on a foam pad, feet heel to the toes with the eyes closed (dominant foot directly in front of the non-dominant foot in tandem)	sc_6

Each condition is scored 1 for a success and 0 for a failure. Because each successive condition is more difficult that the preceding one, the test will be considered complete when the subject fails a condition (after re-test), and the patient will be considered unable to pass the subsequent more difficult conditions, that will be scored as failed conditions.

The total score will be calculated by summing the rate of each condition:

$$Total\ Score = \sum_{i=1}^{6} sc_i$$

Subscores will be calculated for eyes closed on 1 hand

$$Eyes\ closed\ Score = sc_2 + sc_4 + sc_6$$

and eyes open on the other hand

$$Eyes\ open\ Score = sc_1 + sc_3 + sc_5$$

The average scores of the Romberg test in the morning and evening will be used when two assessments are available for the same visit.

6.1.6.4. DHI total score and subscores

The purpose of the Dizziness Handicap Inventory (DHI) scale is to identify the difficulties that the patient may be experiencing because of dizziness. The scale examines 25 questions and 3 domains:

Domain	Number of Questions	Questions
Physical	7	P1, P4, P8, P11, P13, P17, P25
Emotional	9	E2, E9, E10, E15, E18, E20, E21, E22, E23
Functional	9	F3, F5, F6, F7, F12, F16, F19, F24

There are 3 options for each question:

- Always
- Sometimes
- No

The sum of each rating calculated with

- Always = 4
- Sometimes = 2
- No = 0

is the perceived total disability scoring. The total score ranges for 0 (no perceived disability) to 100 (maximum perceived disability).

Subscores for the 3 domains will be calculated. If a single answer is missing the corrisponding subscore and the total score will be missing.

6.1.6.5. VADL total score and subscores

The Vestibular Disorders Activities of Daily Living Scale (VADL) evaluates the effects of vertigo and balance disorders on independence in routine activities of daily living. The scale is a 28 item questionnaire that is broken into 3 subscales: functional, ambulatory, and instrumental:

Domain	Number of Questions	Questions
Functional	12	F1 to F12
Ambulatory	9	A13 to A21
Instrumental	7	I22 to I28

The questionnaire requires to rate self-perceived disablement level on a scale that ranges from 1 (I am not disabled) to 10 (I no longer perform the activity).

The overall score and each subscore are calculated by taking both median and mean values over the relevant quesitons using the following scores.

- INDEPENDENT = 1
- UNCOMFORTABLE, NO CHANGE IN ABILITY = 2
- DECREASED ABILITY, NO CHANGE IN MANNER OF PERFORMANCE = 3
- SLOWER, CAUTIOUS, MORE CAREFUL = 4
- PREFER USING AN OBJECT FOR HELP = 5
- MUST USE AN OBJECT FOR HELP = 6
- MUST USE SPECIAL EQUIPMENT = 7
- NEED PHYSICAL ASSISTANCE = 8
- DEPENDENT= 9
- TOO DIFFICULT, NO LONGER PERFORM = 10

The subscore and the total score will be calculate even if a single answer or more answers are missing or not applicable.

6.1.6.6. Time to unassisted walk

Walking as usual without support will be considered at the first time when the patient is ticking ‘no’ to the question “Because of your vertigo (or disequilibrium) problem, do you have difficulty walking 10 meters (32,8 feet) at your usual speed without using support?” and all further assessments are ‘no’. The time to unassisted walk will be calculated in hours using the following formula:

(date and time of walking as usual without support) - (date and time of baseline visit at H0)

This time will be censored at the day of the end of study visit (D28).

6.1.6.7. WPAI-SHP

The Work Productivity and Activity Impairment – Specific Health Problem (WPAI-SHP) questionnaire measures impairments in work and activities over the past 7 days.

The patient will be requested to fill-in the WPAI-SHP questionnaire at the End-of-Study visit (D28).

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

Questions:

1 = currently employed

2 = hours missed due to specified problem

3 = hours missed other reasons

4 = hours actually worked

5 = degree problem affected productivity while working

6 = degree problem affected regular activities

The following scores will be calculated:

Percent work time missed due to vertigo: 100* Q2/(Q2+Q4)

Percent impairment while working due to vertigo: 100* Q5/10

Percent overall work impairment due to vertigo::

$$100*(Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)])$$

Percent activity impairment due to vertigo: 100*Q6/10

If a single answer is missing the corrisponding subscore and the total score will be missing.

6.1.6.8. Compliance

Study drug intake is planned using the following scheme:

Intake	When
1st	Day 1 H0
2nd	Day 1 H12
3rd	Day 2
4th	Day 3
5th	Day 4

The overall compliance for each subject will be calculated as the number of study drug intakes.

6.1.6.9. Length of hospital stay

The length of hospital stay (in hours) due to AUV or due to SAE will be calculated using the following duration in hours: (discharge date and time – admission date and time).

6.1.6.10. Abnormal and clinically significant results

The information about abnormal results and clinically significant results for laboratory tests will be combined using the following categories:

- Within normal limits

- Abnormal- high and clinically significant
- Abnormal- high, but not clinically significant
- Abnormal- low and clinically significant
- Abnormal- low but not clinically significant

The information about abnormal results and clinically significant results for physical examination tests will be combined using the following categories:

- Normal
- Abnormal

6.1.6.11. Treatment related adverse event

A treatment related AE is any AE with a relationship to the study drug of probable or possible. A non-treatment related AE is any AE with a relationship to the study drug of unlikely or unrelated. An AE with missing or not assessable relationship will be considered as related.

6.1.6.12. Prior and concomitant medications

Medications that started prior to the first study drug intake will be considered prior medications. A concomitant medication is defined as any medication that was administered during the treatment period. This includes medications that started before the treatment period and continued while on treatment and medications that started during the treatment period.

Any medications continuing or starting post the first study drug intake and before the last drug intake will be considered to be concomitant. If a medication starts prior to the first study drug intake and continues after the first study drug intake it will be considered both prior and concomitant.

If the start/stop dates of a medication are partially or completely missing, then the medication will be assumed to be concomitant if it cannot be definitely shown that it was not administered during the treatment period. Missing dates will not be replaced.

6.1.7. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All *P* values will be displayed in four decimals and rounded using standard scientific notation (eg, 0.XXXX). If a *P* value less than 0.0001 occurs it will be shown in tables as <0.0001.

Adverse events will be coded using the MedDRA version 20.0 thesaurus.

7. Study Patients and Demographics

7.1. Disposition of Patients and Withdrawals

All patients who provide informed consent will be accounted for in this study.

The total number of subjects for each of the following categories will be presented for the screened population:

- Screened Population
- Safety Population
- ITT Population
- mITT Population
- PP Population
- Ancillary Population
- Completed patients up to visit 7, Day 28 (±2 days)
- Patients at each visit
- Patients withdrawn
- Reasons for early study termination

In summary tables for disposition of patients, a breakdown by center and randomized treatment groups will be given.

For all categories of patients percentages will be calculated using the number of randomized patients as denominator.

The total number of screening failures and the reasons for screen failure will be presented overall and by center in separate tables.

7.2. Protocol Violations and Deviations

Protocol deviations will be identified and classified at the blinded data review meeting before defining the analysis populations.

Only patients with potentially major deviations will be discussed.

Major protocol violations – i.e. those leading to exclusion from the PP population – will be summarized by type of violations, overall and by center for the ITT population.

Protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Descriptive summaries of the demographic and other baseline characteristics will be completed for each population: ITT, mITT, Safety, and PP.

Descriptive summaries of demographic and other baseline conditions will include:

- Demographics (age, body weight, gender, ethinicty, race)
- Medical history

- Prior medications

Medical history will be coded with MedDRA dictionary. Incidences of findings in medical history will be summarized by system organ class (SOC) and preferred term by treatment groups, unless otherwise specified.

The frequency and percentage of prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 within level 1 by treatment group, unless otherwise specified.

7.4. Exposure and Compliance

Descriptive statistics for the compliance as defined in Section 6.1.6.8 will be presented by treatment group on safety population.

8. Efficacy Analysis

This study will examine the efficacy of SENS-111 on the VI-VAS AUC. Efficacy analyses will be performed based on the treatment group to which the patient was randomized.

The primary and secondary efficacy analyses will be based on the ITT population.

For completeness the analyses will be repeated for the PP population.

The standing VI-VAS, worst VI-VAS, and nausea intensity VAS will be analyzed using an ANCOVA model for the mITT population.

8.1. Primary Efficacy Analysis

The standing VI-VAS will be summarized using descriptive statistics of absolute values and changes from baseline at each mapped time point, and of the AUC including the length of the AUC observation period. Each VAS assessment will be mapped to a time point as follows:

Time point (mapped value)	VAS assessment time since baseline (hours)
12 hours	6 (excluded) to 18 (included)
24 hours	18 (excluded) to 30 (included)
36 hours	30 (excluded) to 42 (included)
…	

When more than one VAS assessment fall within the same time window, then only the VAS assessment closest to the middle point will be assigned to the time point. In case of values that are equidistant to the middle point, the latest assessment only will be assigned to the time point.

VAS assessment not mapped to time point will not be included in the summary statistics and in the MMRM analysis.

The VI-VAS AUC will be compared between treatment groups within an analysis of covariance model (ANCOVA) with the stratification factor duration of vertigo (≤24 hours, >24 hours before being treated) and the baseline VI-VAS as covariates. The two comparisons to placebo (SENS-111 at 100 mg vs placebo, and SENS-111 at 200 mg vs placebo) will be tested for superiority at 5% one-sided significance level, the corresponding 90% two-sided confidence intervals will be presented. In addition the pool of the two active doses (SENS-111 at 100 mg and SENS-111 at 200 mg) will also be tested for superiority at 5% one-sided significance level, and the corresponding 90% two-sided confidence interval will be presented.

A sensitivity analysis using the date/time of the first dose intake of randomized study drug as the time reference for the AUC calculation will also be performed. In this analysis, the baseline will be defined as the last observation recorded in the ePRO until the time of the first dose intake and the AUC calculation will conducted as defined in section 6.1.6.2 (using all VAS assessments between baseline and baseline + 102 hours). This analysis will be conducted on the mITT and the PP restricted to subjects for whom the baseline standing VI-VAS based on first study drug intake is available and ≥ 60 mm.

A sensitivity analysis excluding patients who received treatment related to AUV over the last 3 months prior to the enrollment will also be performed.

As a complementary analysis in order to get a better insight of the treatment effect over time, the 8 post baseline VI-VAS scores at mapped time points (12h, 24h, 36h, 48h, 72h, 84h, 96h) will be analyzed, without replacement of missing values, using a restricted maximum likelihood (REML) based repeated measures approach. The same analysis using baseline and mapped time points both defined with reference to time of first dose intake will be applied on the mITT and the PP restricted to subjects for whom the baseline standing VI-VAS based on first study drug intake is available and ≥ 60 mm.

Analyses will include the fixed, categorical effects of treatment, time, and treatment-by-time interaction, as well as the binary stratification factor (duration of vertigo before being treated) and the continuous, fixed covariates of baseline VI-VAS and baseline score-by-time interaction.

An unstructured covariance structure will be used to model the within-patient errors. If this analysis fails to converge, simpler structures (e.g. first-order ante-dependent or heterogeneous compound symmetry structures) will be tested in a model without treatment effect; the covariance structure converging to the best fit, as determined by Akaike's information criterion, will be used in the full model. Only the final model will be included in the report.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Within this model the test of interest will be the treatment-by-time interaction performed at significance level of 5%. In a second step, the 2 comparisons to placebo will be tested at each time at 5% one-sided significal level and the corresponding 90% two-sided confidence intervals will be presented.

The same MMRM approach will be repeated using all mapped time points up to 672 h (D28) included. This additional analysis will provide some information on the long-term recovery of the vestibular function.

8.2. Secondary Efficacy Analysis

8.2.1. Worst spontaneous vertigo intensity over the 4 treatment days

The worst VI-VAS will be summarized using descriptive statistics of absolute values and changes from baseline at each assessment and of AUC including the length of the AUC observation period.

The AUC for the worst VI-VAS using the baseline and first 8 post baseline assessments will be analyzed using the approach described in Section 8.1 for the primary endpoint.

8.2.2. Nausea severity over the four treatment days

The Nausea Intensity VAS will be summarized using descriptive statistics of absolute values and changes from baseline at each assessment and of AUC including the length of the AUC observation period.

The AUC for the Nausea Intensity VAS using the baseline and first 8 post-baseline assessments will be analyzed using the approach described in Section 8.1 for the primary endpoint.

8.2.3. Change from baseline of the total score of the Romberg tests at the end of treatment and end of study

The total score and subscores of the Romberg test will be summarized using descriptive statistics at the following visits: baseline, end of treatment (D5), end of study (D28).

The change from baseline of the total score of the Romberg tests at the end of treatment visit (D5) will be compared between treatment groups within an analysis of covariance model. Patients without data available at the end of treatment will be excluded from the analysis. The covariates will be the stratification factor, duration of vertigo (≤24 hours, >24 hours) before being treated and the baseline total score. The 2 comparisons to placebo will be tested at 5% one-sided significance level, the corresponding two-sided 90% confidence interval will be presented.

The same approach will be applied to the change from baseline at the end of study (D28).

8.2.4. Peak slow phase velocity at the end of treatment and end of study

The mean and the peak of the slow phase velocity will be summarized using descriptive statistics at the following visits: baseline, end of hospitalization, end of treatment (D5), end of study (D28).

The change from baseline of the peak slow phase velocity (degrees/second) at the end of treatment visit (D5) and the change from baseline at the end of study (D28) will be analyzed using the approach described in Section 8.2.3 for the Romberg tests.

The analysis for the peak slow phase velocity will be repeated for each testing condition: no fixation (30 sec) and fixation (10 sec).

8.2.5. Functional disability at the end of study

The DHI total score and subscores will be summarized using descriptive statistics by visit.

The change from baseline of the DHI functional subscore scale at the end of study (D28) will be compared between treatment groups using the approach described in Section 8.2.3 for the Romberg tests. Patients without data available at the end of study will be excluded from the analysis. The 2 comparisons to placebo will be tested at 5% one-sided significance level, the corresponding two-sided 90% confidence interval will be presented.

The VADL total score and subscores at the end of the study (D28) will be described using summary statistics.

8.3. Exploratory Efficacy Analysis

8.3.1. The caloric test

The caloric test at baseline and end of study visit (D28) will be performed in some centers participating in an ancillary study. The total response (TR), i.e. the absolute sum of all appropriately directed responses, and the relative vestibular reduction (RVR) will be analyzed using descriptive summaries for each visit.

8.3.2. The video Head Impulse Test

The video Head Impulse Test will be conducted at baseline to confirm the peripheral origin of the vertigo. An additional test at the end of treatment visit (D5) and end of study visit (D28) will be performed in some centers participating in an ancillary study. The vHIT provides a quick and objective measure of the vestibular ocular reflex (VOR).

The VOR parameter will be analyzed using descriptive summaries for each visit.

8.3.3. Time to unassisted walking

Time to unassisted walking from Day 1, i.e. Visit 2 Inclusion H0, in days will be analyzed using a descriptive time-to-event approach (Kaplan-Meier).

Summaries will include the number of patients experiencing the event and the number of patients censored; the median, lower quartile and upper quartile estimates of time-to-event; and point estimates for the event-free rate at each visit.

A Kaplan–Meier graph of time to unassisted walk by treatment group will be presented. The null hypothesis of no difference between pairwise comparisons SENS111 100 mg vs placebo, and SENS111 200 mg vs placebo will be tested using a log-rank test with a 5% one-sided significance level. A Cox proportional hazard regression model with a categorical variable for the treatment arm as independent variable will also be used to estimate the hazard ratios for the treatment effects (SENS111 100 mg vs placebo, and SENS111 200 mg vs placebo), which will

be presented together with two sided 90% confidence intervals, as well as the corresponding P value.

Time to unassisted walk will also be analyzed fitting a Cox proportional hazard regression with a categorical variable for the treatment arm as independent variable and the stratification factor duration of vertigo (≤24 hours, >24 hours before being treated) as covariate. The hazard ratio for the treatment effects (SENS111 100 mg vs placebo, and SENS111 200 mg vs placebo) will be presented together with two sided 90% confidence intervals, as well as the corresponding P value.

9. Safety and Tolerability Analysis

All safety analyses will be performed on the Safety population using descriptive statistics. No inferential statistical tests will be performed.

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each patient:

- Adverse events, treatment-emergent AEs (TEAEs), and serious AEs (SAEs)
- Clinical laboratory investigations (hematology, chemistries, C-reactive protein, βhCG in women)
- Vital signs (blood pressure, heart rate, respiratory rate, body temperature)
- Physical examination
- 12-lead electrocardiograms (ECG)
- Neuro-otologic examination
- AUV diagnosis
- Hospitalization due to AUV

9.1. Adverse Events

A summary table will present:

- All AEs
- AEs leading to withdrawal from the study
- Non Treatment emergent adverse events (non TEAEs)
- Treatment emergent adverse events (TEAEs)
- TEAEs related to study drug
- Mild TEAEs
- Moderate TEAEs
- Severe TEAEs
- Serious TEAEs

- Serious related TEAEs
- TEAEs resulting in death

Separate summaries of treatment-emergent AEs (TEAEs) will be generated by SOC and preferred terms for the following:

- All TEAEs
- All TEAEs by severity
- TEAEs by relationship to study medication

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of AEs leading to withdrawal of study drug, by treatment group, SOC, and preferred term will be prepared.

A data listing of AEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the e-CRF.

9.1.2. Deaths and Serious Adverse Events

Any deaths that occur during the study and serious adverse events will be listed and tabulated by system organ class and preferred term.

9.2. Clinical Laboratory Evaluations

Laboratory values will be displayed in the data listings and those that are outside the normal range will be flagged, along with corresponding normal ranges.

Shift table will be presented to show any change from baseline in the clinical laboratory findings. In the shift table the number and percentages of clinical laboratory test values that are within the limit, low and not clinical significant, low and clinical significant, high and not clinical significant, high and clinical significant will be tabulated by treatment group and visit.

9.3. Vital Signs

Descriptive summaries of absolute values and change from baseline visit will be calculated for each of the following visits:

- V2, Day 1, H0
- V2, Day 1, H12
- V3, Day 2, H24
- V4, end of hospitalization
- V5, Day 5, end of treatment
- V7, Day 28, end of study

and for each of the following parameters:

- temperature (T)
- supine measurements of respiratory rate (RR), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP)
- standing measurements of respiratory rate (RR), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP)

9.4. Electrocardiograms

Descriptive summaries will be presented by visit for the 12-lead ECG measures of heart rate, PR interval, QRS interval, QT interval, QTcF and QTcB interval (both correction methods).

The number and percentage of patients with normal, abnormal not clinically significant, and abnormal clinically significant ECG results will be summarized by treatment group and by visit .

Categorical analyses of the following ECG parameters will be provided by visit and overall showing the number and percentage of patients per treatment group and overall meeting or exceeding some predefined upper limit value:

- PR interval <100 msec
- PR interval >210 msec
- QRS interval <50 msec
- QRS interval >120 msec
- Absolute QTc interval <340 msec
- Absolute QTc interval >450 msec
- Absolute QTc interval >480 msec
- Absolute QTc interval >500 msec
- QTc interval increases from baseline >30 msec
- QTc interval increases from baseline >60 msec
- Heart rate <50 bpm (sinus bradycardia)
- Heart rate >120 bpm (sinus tachycardia)

9.5. Further Safety Evaluations

9.5.1. Physical Examination

The number and percentage of abnormalities will be tabulated by visit in each body system: general appearance, skin and mucous, ears/nose/throat, pulmonary, cardiac, gastro-intestinal, neurological, and other.

9.5.2. Neuro Otologic Examination

The number and percentage of abnormalities will be tabulated by visit for: mental status, cranial nerves, eye movements (and presence of nystagmus), muscle strength and tone, sensory function, coordination, gait, reflexes, external ear, and tympanic membrane/middle ear.

9.5.3. AUV diagnosis

The presence of conditions other than AUV diagnosis, its corresponding examination (CT scan, MRI scan, other), and the side concerned (right, left, both) will be described by treatment group and visit. Moreover the number of patients with another diagnosis than AUV confirmed will be summarized irrespective of study visit.

9.5.4. Hospitalization due to AUV

Hospitalization due to AUV (including participation in the study), the type of ward, and the length of hospital stay will be summarized by treatment arm.

9.5.5. Hospitalization due to Serious Adverse Event

Hospitalization due to SAE, the type of ward, and the length of hospital stay will be summarized by treatment arm.

9.6. Concomitant Medication

Prior medications will be presented separately from concomitant medications.

Medications will be coded using WHODD (Version 1-Sep-2016).

The frequency and percentage of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 within level 1 by treatment groups, unless otherwise specified.

10. Changes from Planned Analysis

The Screened Population, the modified Intention-to-Treat Population and the Ancillary Population are not described in the protocol and they have been added in Section 5.

The efficacy analysis for the mITT population was not planned in the protocol.

The PP Population definiton has been amended. Patients with major protocol deviations are excluded from the PP Population in the protocol, while patients with major protocol deviation likely to impact the primary efficacy endpoint are excluded from the PP Population in this SAP.

There are 3 options for each question of the DHI scale. The option ‘yes’ in the protocol and in the electronic patient reported outcomes data should be amended with ‘always’.

In the AUC calculation, missing final measurements will be replaced by LOCF if the reason for missing data is nausea, other or unknown. The option ‘unknown’ was not included in the protocol.

The change from baseline of the VADL score will not be analyzed since the VADL score is not measured at baseline. The VADL score at the end of study (D28) will be anlayzed using descriptive summary.

11. Other Planned Analysis

11.1. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

The WPAI-SHP questionnaire findings will be presented using descriptive statistics of the following scores:

- Percent work time missed due to vertigo
- Percent impairment while working due to vertigo
- Percent overall work impairment due to vertigo
- Percent activity impairment due to vertigo

These summaries will be presented by treatment group for the ITT Population.

11.2. Pharmacokinetic Analysis

No derivation of PK parameters is planned for this study as a full PK profile is not measured.

However, plasma exposure to SENS-111 will be characterized describing summary statistics of plasma concentration of SENS-111 by treatment arm and visit.

12. References

1. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.

2. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm

3. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.

13. Tables, Listings, and Figures

All listings, tables, and graphs will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

13.1. Planned Table Descriptions

The following are planned summary tables for protocol SENS 111-201. Tables will be numbered according to the nomenclature used to support the clinical study report (CSR) when the [redacted] CSR template is used. However, the table numbering structure can be modified per the sponsor's request to meet compatibility with the sponsor's CSR template.

Table 3 Planned Tables

Table Number	Population(s)	Table Title / Summary	Supporting listing	Requested for the Top-Line Results *
14.1 Demographic Data				
14.1.1.1.1	Enrolled	Summary of Patient Enrollment and Disposition	16.2.1.1 16.2.1.2	Yes
14.1.1.1.2	Enrolled	Summary of Patient Enrollment and Disposition by Center	16.2.1.1 16.2.1.2	No
14.1.1.2.1	Screen Failures	Summary of Reasons for Screening Failure	16.2.1.3	No
14.1.1.2.2	Screen Failures	Summary of Reasons for Screening Failure by Center	16.2.1.3	No
14.1.2.1	ITT	Summary of Major Protocol Deviations	16.2.2.1	No
14.1.2.2	ITT	Summary of Major Protocol Deviations by Center	16.2.2.1	No
14.1.3	ITT, mITT, PP, SAF	Summary of Demographic Data	16.2.4.1	Yes
14.1.4	ITT, mITT, PP, SAF	Medical History by System Organ Class and Preferred Term	16.2.4.2	No
14.1.5	ITT, mITT, PP, SAF	Prior Medications by ATC Level 2	16.2.4.3	No
14.2 Efficacy Tables				
14.2.1.1	ITT, mITT, PP	Summary of Standing VI-VAS Assessments: Absolute Values	16.2.6.1	Yes
14.2.1.2	ITT, mITT, PP	Summary of Standing VI-VAS Assessments: Changes from Baseline	16.2.6.1	Yes
14.2.1.3	ITT, mITT, PP	Summary of AUC for Standing VI-VAS	16.2.6.1	Yes
14.2.1.4.1	ITT, mITT, PP	Statistical Analysis of AUC for Standing VI-VAS: ANCOVA	16.2.6.1	Yes
14.2.1.4.2	ITT, PP	Statistical Analysis of AUC for Standing VI-VAS: ANCOVA excluding patients who received treatment related to AUV	16.2.6.1	Yes
14.2.1.5	ITT, PP	Statistical Analysis of Standing VI-VAS: MMRM (12H to 96H	16.2.6.1	Yes
14.2.1.6	ITT, PP	Statistical Analysis of Standing VI-VAS: MMRM (12H to 672H)	16.2.6.1	No
14.2.1.7	mITT, PP	Sensitivity Analysis of AUC for Standing VI-VAS: ANCOVA	16.2.6.1	No

Table Number	Population(s)	Table Title / Summary	Supporting listing	Requested for the Top-Line Results *
14.2.1.8	mITT, PP	Sensitivity Analysis of Standing VI-VAS: MMRM (12H to 96H)	16.2.6.1	No
14.2.2.1	ITT, mITT, PP	Summary of Worst VI-VAS Assessments: Absolute values	16.2.6.2	Yes
14.2.2.2	ITT, mITT, PP	Summary of Worst VI-VAS Assessments: Changes from Baseline	16.2.6.2	Yes
14.2.2.3	ITT, mITT, PP	Summary of AUC for Worst VI-VAS	16.2.6.2	Yes
14.2.2.4.1	ITT, mITT, PP	Statistical analysis of AUC for Worst VI-VAS: ANCOVA	16.2.6.2	Yes
14.2.2.4.2	ITT, PP	Statistical analysis of AUC for Worst VI-VAS: ANCOVA excluding patients who received treatment related to AUV	16.2.6.2	Yes
14.2.2.5	ITT, PP	Statistical analysis of Worst VI-VAS: MMRM (12H to 96H)	16.2.6.2	Yes
14.2.2.6	ITT, PP	Statistical analysis of Worst VI-VAS: MMRM (12H to 672H)	16.2.6.2	No
14.2.2.7	mITT, PP	Sensitivity Analysis of AUC for Worst VI-VAS: ANCOVA	16.2.6.2	No
14.2.2.8	mITT, PP	Sensitivity Analysis of Worst VI-VAS: MMRM (12H to 96H)	16.2.6.2	No
14.2.3.1	ITT, mITT, PP	Summary of Nausea Intensity VAS Assessments: Absolute Values	16.2.6.3	No
14.2.3.2	ITT, mITT, PP	Summary of Nausea Intensity VAS Assessments: Changes from Baseline	16.2.6.3	No
14.2.3.3	ITT, mITT, PP	Summary of AUC for Nausea Intensity VAS	16.2.6.3	No
14.2.3.4.1	ITT, PP	Statistical Analysis of AUC for Nausea Intensity VAS: ANCOVA	16.2.6.3	No
14.2.3.4.2	ITT, PP	Statistical Analysis of AUC for Nausea Intensity VAS: ANCOVA excluding patients who received treatment related to AUV	16.2.6.3	No
14.2.3.5	ITT, PP	Statistical Analysis of Nausea Intensity VAS: MMRM (12H to 96H)	16.2.6.3	No
14.2.3.6	ITT, PP	Statistical Analysis of Nausea Intensity VAS: MMRM (12H to 672H)	16.2.6.3	No
14.2.3.7	mITT, PP	Sensitivity Analysis of AUC for Nausea Intensity VAS: ANCOVA	16.2.6.3	No

Table Number	Population(s)	Table Title / Summary	Supporting listing	Requested for the Top-Line Results *
14.2.3.8	mITT, PP	Sensitivity Analysis of Nausea Intensity VAS: MMRM (12H to 96H)	16.2.6.3	No
14.2.4.1	ITT, PP	Summary of the Total Score and Subscores of the Romberg Test: Absolute Values	16.2.6.4	No
14.2.4.2	ITT, PP	Summary of the Total Score and Subscores of the Romberg Test: Changes from Baseline	16.2.6.4	No
14.2.4.3	ITT, PP	Statistical Analysis of the Total Score of the Romberg Test: ANCOVA	16.2.6.4	No
14.2.5.1	ITT, PP	Summary of the Average and Peak Slow Phase Velocity: Absolute Values	16.2.6.5	No
14.2.5.2	ITT, PP	Summary of the Average and Peak Slow Phase Velocity: Changes from Baseline	16.2.6.5	No
14.2.5.3	ITT, PP	Statistical Analysis of the Peak Slow Phase Velocity: ANCOVA	16.2.6.5	No
14.2.6.1	ITT, PP	Summary of the Total Score and Subscores of the DHI test: Absolute Values	16.2.6.6	No
14.2.6.2	ITT, PP	Summary of the Total Score and Subscores of the DHI test: Changes from Baseline	16.2.6.6	No
14.2.6.3	ITT, PP	Change from Baseline of the DHI Functional Subscore Scale at the End of Study Visit: ANCOVA	16.2.6.6	No
14.2.7	ITT, PP	Summary of the Total Score and Subscores of the VADL Test: Absolute Values	16.2.6.7	No
14.2.8	ANC	Summary of the Total Response (TR) and the Relative Vestibular Reduction (RVR): Absolute Values	16.2.6.8	No
14.2.9	ANC	Summary of Video-head Impulse Test: Absolute Values	16.2.6.9	No
14.2.10.1	ITT, PP	Statistical Analysis of Time to Unassisted Walk: Event-free Rates by Time	16.2.6.10	No
14.2.10.2	ITT, PP	Statistical Analysis of Time to Unassisted Walk: Median and Quartile Estimates of the Event-free Time	16.2.6.10	No
14.2.10.3	ITT, PP	Log-rank Test for Time to Unassisted Walk: Comparison between Treatment Groups	16.2.6.10	No

Table Number	Population(s)	Table Title / Summary	Supporting listing	Requested for the Top-Line Results *
14.2.10.4	ITT, PP	Hazard Ratios of Time to Unassisted Walk: Comparison between Treatment Groups (with Covariate Stratification Factor Duration of Vertigo)	16.2.6.10	No
14.2.11	ITT	Summary of the WPAI-SHP Scores	16.2.6.11	No
14.3 Safety and Tolerability Tables				
14.3.1 Displays of Adverse Events				
14.3.1.1	SAF	Summary of all Adverse Events	16.2.7.1	No
14.3.1.2	SAF	Treatment Emergent Adverse Events by System Organ Class and Preferred Term	16.2.7.1	No
14.3.1.3	SAF	Treatment Emergent Adverse Events by Severity, System Organ Class, and Preferred Term	16.2.7.1	No
14.3.1.4	SAF	Treatment Emergent Adverse Events by Relationship to study medication, System Organ Class, and Preferred Term	16.2.7.1	No
14.3.2 Other Serious and Significant Adverse Events				
14.3.2.2	SAF	Adverse Events Leading to Withdrawal from the Study by System Organ Class and Preferred Term	16.2.7.3	No
14.3.2.3	SAF	Treatment Emergent Adverse Events Resulting in Death by System Organ Class and Preferred Term	16.2.7.4	No
14.3.2.3	SAF	Serious Adverse Events by System Organ Class and Preferred Term	16.2.7.2	No
14.3.5 Laboratory Data Tables				
14.3.5.1	SAF	Shift Table of Clinical Chemistry Results	16.2.8.1	No
14.3.5.2	SAF	Shift Table of Hematology Results	16.2.8.2	No
14.3.6 Other Safety and Tolerability Tables				
14.3.6.1.1	SAF	Vital Signs Results: Absolute Values	16.2.9.1	No
14.3.6.1.2	SAF	Vital Signs Results: Changes from Baseline	16.2.9.1	No
14.3.6.2.1	SAF	ECG Results	16.2.9.2	No

Table Number	Population(s)	Table Title / Summary	Supporting listing	Requested for the Top-Line Results *
14.3.6.2.2	SAF	ECG Results: Categorical Analysis	16.2.9.2	No
14.3.6.3	SAF	Abnormalities and Clinical Significance in Physical Examination Results	16.2.9.3	No
14.3.6.4	SAF	Abnormalities in Neuro Otologic Examination	16.2.9.4	No
14.3.6.5	SAF	Diagnosis of AUV	16.2.9.5	No
14.3.6.6	SAF	Hospitalization due to AUV (including participation in the study)	16.2.9.6	No
14.3.6.7	SAF	Hospitalization due to Serious Adverse Event	16.2.9.7	No
14.3.6.8	SAF	Concomitant Medication by ATC Level 2	16.2.4.3	No
14.3.6.9	SAF	Compliance	16.2.5.1	No
14.3.6.10	SAF	Summary of Plasma Concentration Levels	16.2.5.2	No

13.2. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol 2.0. Data listings will be numbered according to the nomenclature used to support the CSR when the [redacted] CSR template is used. However, the listing numbering structure can be modified per the sponsor's request to meet compatibility with the sponsor's CSR template.

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, site, and subject number. All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (eg, repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Table 4 Planned Listings

Data Listing Number		Data Listing Title / Summary
16.2.1 Patient Discontinuation/Completion		
16.2.1.1		Assignment to Analysis Populations and Treatment Group
16.2.1.2		Study Completion Status
16.2.1.3		List of Reasons for Screening Failure
16.2.2 Protocol Deviations		
16.2.2.3		Major Protocol Deviations
16.2.3 Patients Excluded from the Efficacy Analysis		
16.2.3.4		List of Patients Excluded from Analysis Populations
16.2.4 Demographic Data and Other Baseline Characteristics		
16.2.4.5		Demographic data
16.2.4.6		Medical History
16.2.4.7		Prior and Concomitant Medications
16.2.5 Drug Compliance and Concentration Data		
16.2.5.8		Drug Accountability
16.2.5.2		Plasma Concentration Levels
16.2.6 Individual Efficacy Response Data		
16.2.6.9		Standing VI-VAS
16.2.6.2		Worst VI-VAS

Data Listing Number		Data Listing Title / Summary
16.2.6.3		Nausea Intensity VAS
16.2.6.4		Romberg test
16.2.6.5		Video Oculography
16.2.6.6		Dizziness Handicap Inventory (DHI) test
16.2.6.7		Vestibular Disorder Activities of Daily Living Scale (VADL) Test
16.2.6.8		Caloric Test
16.2.6.9		Video-head Impulse Test
16.2.6.10		Unassisted Walk
16.2.6.11		Work Productivity and Activity Impairment (WPAI-SHP)
16.2.7 Adverse Event Listings		
16.2.7.10		Adverse Events
16.2.7.2		Serious Adverse Events
16.2.7.3		Adverse Events Leading to Withdrawal
16.2.7.4		Deaths
16.2.8 Laboratory Data Listings		
16.2.8.11		Clinical Chemistry Results
16.2.8.12		Hematology Results
16.2.8.3		Pregnancy test results
16.2.9 Listings of Other Clinical Observations and Measurements		
16.2.9.13		Vital Signs Results
16.2.9.14		ECG Results
16.2.9.15		Physical Examination Results
16.2.9.4		Neuro Otologic Examination Results
16.2.9.5		Diagnosis of AUV
16.2.9.6		Hospitalization due to AUV (including prticipation in thestudy)
16.2.9.7		Hospitalization due to Serious Adverse Events
16.2.9.8		CT Scan and MRI Scan

13.3. Planned Figure Descriptions

The following are planned summary figures for protocol number SENS 111-201. The figure numbers and page numbers are placeholders only and will be determined when the figures are produced.

Table 5 Planned Figures

Figure Number	Population	Figure Title / Summary	Supporting table or listing
14.4.1	ITT	Kaplan Meier graph of time to unassisted walk	14.2.26

14. Tables, Listings, and Listing Shells

14.1. Standard Layout for all Tables, Listings, and Figures

Table and listing shells are provided as a separate document. The final statistical tables will be produced in the format of the shells and will additionally include “double” page numbering in the format “page xx of yy”. Note that programming notes may be added or modified if appropriate after each TLF shell.

The final statistical output will be provided as fully bookmarked pdf file including a table of contents.

No shells are provided for figures.

Appendix 1: [redacted] Library of Abbreviations

Abbreviation	Definition
AE	adverse event
ANC	ancillary population
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
AUC	area under the curve
AUV	acute unilateral vestibulopathy
BOCF	baseline observation carried forward
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
D	day
DBP	diastolic blood pressure
DHI	dizziness handicap inventory
DMC	data monitoring committee
eCRF	electronical case report form
ECG	electrocardiogram
EMA	European medicines agency
FDA	food and drug administration
GLM	generalized linear model

Abbreviation	Definition
HR	heart rate
ICH	international conference on harmonisation
ITT	Intention-to-treat population
IWRS	Interactive web system response
LOCF	last observation carried forward
MedDRA	medical dictionary for regulatory activities
MRI	magnetic resonance imaging
NI-VAS	nausea intensity visual analogue scale
ODT	orally disintegrating tablet
PD	pharmacodynamics
PP	Per-protocol population
PK	pharmacokinetics
QTc	QT-interval for ECG corrected for heart rate
REML	restricted maximum likelihood
RR	respiratory rate
RVR	relative vestibular reduction
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SAF	safety population

Abbreviation	Definition
SOC	system organ class
SPV	slow phase velocity
T	temperature
TEAE	treatment-emergent adverse event
TR	total response
VADL	vestibular disorders activities of daily living
vHIT	video-head impulse test
VAS	visual analogue scale
VI-VAS	vertigo intensity visual analogue scale
VOG	videooculography
VOR	vestibular ocular reflex
WHO	world health organization
WPAI-SHP	work productivity and activity impairment questionnaire – specific health problem