AMENDED CLINICAL TRIAL PROTOCOL

STUDY COMPOUND: SENS-111

STUDY Number: SENS 111-201

NCT03110458

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

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CLINICAL TRIAL PROTOCOL APROVAL FORM

The protocol, entitled: “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 “ has been reviewed and approved by:

and I have fully discussed the objectives of this clinical trial and the contents of this protocol with the Sponsor's representative(s).

I agree to conduct the clinical trial according to this protocol and to comply with its requirements, subject to ethical and safety considerations.

I understand that, should the decision be made by the Sponsor to terminate prematurely or suspend the clinical trial at any time for whatever reasons, such decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the clinical trial I will communicate immediately such decision in writing to the Sponsor.

INVESTIGATOR/ International Coordinator

[redacted]

[redacted]

FOR THE SPONSOR

[redacted]

[redacted]

[redacted]

1 TABLE OF CONTENT

2 LIST OF ABBREVIATIONS

AE: adverse event
AUC: area under the curve
AUV: acute unilateral vestibulopathy
BP: blood pressure
BPPV: benign paroxysmal positional vertigo
CBC: complete blood count
Cmax: maximum concentration
CNS: central nervous system
CRF: case report Form
CRP: C reactive protein
CSR: clinical study report
CYP: cytochrome
DB: double blind
DDI: drug drug interaction
DHI: disability handicap Index
ECG: electrocardiogram
F: fraction
GLP: good Laboratory Practice
H: histamine
H_4R: Histamine 4 receptor
Hb: hemoglobin
Hct: hematocrit
HIT: head impulse test
HR: heart rate
IEC: independent ethics committee.
IRB: institutional review board.
ITT: Intent to treat
LOAEL: lowest observed adverse effect level
LOCF: last observation carried forward
MedDRA: medical dictionnary of regulatory affairs
MRI: magnetic resonance imaging
NOAEL: no observed adverse effect level
ODT: orally dispersible tablet
PK: pharmacokinetic
PP: per protocol
R: randomized
SAE: serious adverse event

SP: sway path
TEAE: treatment-emergent adverse event.
VADL: vestibular disorder activities of daily living scale
VAS: visual analog scale
VI-VAS: vertigo intensity visual analog scale
VOR: vestibulo-ocular reflex
WBC: white blood count
WOCBP: woman of child-bearing potential

3 CLINICAL TRIAL SUMMARY

NAME OF COMPANY: Sensorion	NAME OF FINISHED PRODUCT: NA®	NAME OF ACTIVE INGREDIENT: SENS-111
Study Title: A multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 2 dose-regimens of orally administered SENS-111 (100mg and 200mg) given during 4 days in patients suffering from Acute Unilateral Vestibulopathy (AUV)		
Study Code Numbers: SPONSOR ref.: SENS 111-201		
International Coordinator: Michael Strupp, MD, FANA, FEAN, Prof. of Neurology (Munich, Germany)		
Clinical Study Sites: 28 sites in Asia; Australia; Europe; US		
Objectives: **Primary objective:** • To demonstrate the efficacy of SENS-111 in Acute Unilateral Vestibulopathy (AUV) **Secondary objectives:** • 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		
Methodology/Study Design: Multicenter, double-blind, randomized, placebo-controlled 3 parallel arm study comparing SENS-111 (100 mg or 200 mg) to placebo Treatment administered once daily for 4 days with an additional dose 12 hours after the first dose intake.		

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Number of Subjects:

Randomised: 207 (69 patients/ treatment group)

Randomization 1:1:1, stratified by duration of vertigo before being treated (≤ 24 hours, > 24 hours)

Diagnosis and Main Criteria for Inclusion:

Strict adherence to the inclusion and exclusion criteria is critical to ensure that only patients suffering from AUV are included.

Inclusion criteria:

1. Male or female
2. Aged ≥18 years and <75 years
3. Suffering from an acute episode of vertigo of peripheral origin defined as:
    a. Severe (≥ 60mm on the standing vertigo intensity visual analog scale)
    b. Prolonged (more than 6 hours),
    c. Associated with imbalance (and/or postural imbalance) and nausea (and/or vomiting)
    d. Spontaneous nystagmus toward the unaffected ear (fast phase) which is suppressed or reduced by visual fixation confirmed by oculography
    e. Gain of the vestibulo ocular reflex (VOR) <0.7, measured by the video- head impulse test (HIT) and/or difference between the 2 labyrinths >25% according to the caloric test (de Jongkees' formula).
4. Affiliated or is a beneficiary to a health insurance system (if applicable per national regulations)
5. Signed and dated written informed consent.

Exclusion criteria: Patients with the following criteria must not be included

1. Vertigo duration of less than 6 hours before randomization
2. Acute continuous vertigo lasting more than 72 hours prior to randomization
3. Acute hearing loss during or after the onset of vertigo.
4. Acute unilateral tinnitus during or after the onset of vertigo

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5. History of acute or chronic vestibular diseases (including Ménière's disease, acute labyrinthitis, vestibular migraine...), vestibular dysfunction, previous episode of acute unilateral vestibulopathy or prolonged vertigo.
6. Ongoing Benign paroxysmal positional vertigo (BPPV)
7. History of prior acute central vestibular lesion.
8. Acute or chronic disease of middle ear (infections, otitis)
9. Concurrent Varicella Zoster Virus (VZV) ear infection (Herpes zoster oticus)
10. History of cochlear implants
11. Neurological disorders including stroke, brainstem or cerebellar dysfunction within the last 3 months (In case of possible stroke of the brainstem or cerebellum, the diagnosis should have been excluded by a MRI performed within the last 48 hours)
12. Past or concomitant treatment with ototoxic chemotherapy
13. Past history of seizures or convulsions
14. Head trauma within the last 10 days prior to randomization
15. Aminoglycosides in the past 6 months given via systemic or transtympanic administration
16. Concomitant treatment with any of the followings within the last 24 hours prior to randomization if more than 2 doses have been taken:
    a. Antihistamines: diphenhydramine, cyclizine, dimenhydrinate, meclizine, hydroxyzine, promethazine,
    b. Cinnarizine, flunarizine
    c. Central anti-dopaminergics: neuroleptics, unless the dose is stable for at least 1 month prior to randomization and no changes are expected during the course of the study
    d. Benzodiazepines
    e. Histaminergics (e.g., betahistine)
    f. Scopolamine, homatropine
    g. Gabapentin, pregabalin
    h. Acetylleucine, 5HT3 antagonists (ondensetron, granisetron, palonosetron etc…)

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i. Piracetam, piribedil, trimetazidine,

j. Corticosteroids (oral or injectable) unless the dose is stable for at least 1 month prior to randomization and no changes are expected during the course of the study

17. Treatment with any investigational agent within 4 weeks prior to randomization or 5 half-lives of the investigational drug (whichever is longer)
18. Prior participation in a clinical trial with SENS-111
19. History of malignancy other than effectively treated carcinoma in-situ of the cervix, or adequately treated non-metastatic squamous or basal cell carcinoma of the skin, within 5 years
20. Known history of, or concomitant severe hepatic, gastrointestinal, cardiovascular, respiratory, neurological, psychiatric, hematological, renal, or dermatological disease, or any condition, psychiatric, substance abuse, or otherwise, that, in the opinion of the Investigator might interfere with the evaluation of study treatment or warrant exclusion.
21. Pregnancy (a negative pregnancy test is required for all women of childbearing potential (WOCBP) before initiation of treatment
22. Male and female patients of child-bearing potential who are unwilling to use an highly effective contraception while enrolled on study and receiving the experimental drug, and for at least 1 month after the last intake of the investigational product. Highly effective therapy includes:

    a. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal or transdermal

    b. progestogen-only hormonal contraception associated with inhibition of ovulation 1 : oral, injectable or implantable

    c. intrauterine device (IUD)

    d. intrauterine hormone-releasing system (IUS)

    e. bilateral tubal occlusion

    f. vasectomised partner

    g. sexual abstinence

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(see appendix 11 for complete guidance)

23. Nursing mothers
24. Severe abnormal laboratory findings
    a. Creatininemia >1.5 upper limit of normal (ULN))
    b. INR >1.7 ULN, Total bilirubin >2 ULN
    c. ALAT and/or ASAT > 3 x ULN
    d. Hemoglobin <0.9 Giga/L and/or
    e. Neutrophils <1,5 Giga/L and/or
    f. Platelets <100 Giga/L
25. Patients who, in the opinion of the Investigator, have significant medical or psychosocial findings that warrant exclusion. Examples of significant problems include, but are not limited to other serious non-malignancy-associated medical conditions that may be expected to limit life expectancy or significantly increase the risk of serious adverse event (SAEs) and any condition, psychiatric, substance abuse, or otherwise, that, in the opinion of the Investigator, would preclude informed consent, consistent follow-up, or compliance with any aspect of the study
26. Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

Test Product:

Product name: SENS-111

Unit dose: 100 mg Oral Dispersible Tablet (ODT)

Regimen: Once a day for 4 days + one additional dose 12 hours after first intake

Mode/route: Oral. The drug should be kept in the mouth until complete dispersion

Drug Being Tested, Dose, Method of Administration:

SENS-111 100mg: 2 ODT (1 ODT SENS-111 and 1 ODT placebo)

SENS-111 200mg: 2 ODTs SENS-111

Placebo: 2 placebo ODTs

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Duration of Treatment: 4 days

Criteria for Evaluation:

Primary endpoint:

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

Main secondary efficacy endpoints: comparison between groups of

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

Exploratory efficacy endpoints: comparison between groups of

- Vertigo Intensity while standing and worst spontaneous at the end of the study (Day 28) assessed by the Vertigo Intensity VAS.
- Time to unassisted walk assessed by a specific question.

Safety Endpoints

- Adverse events, laboratory, vital signs and ECG

Health Economic end-point:

- Health economic evaluation assessed with the Work Productivity and Activity Impairment (WPAI-SH) questionnaire at the end of study

Pharmacokinetics:

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- SENS-111 pharmacokinetic parameters

Data Monitoring Committee (DMC):

An independent DMC will be organized to regularly evaluate the safety of SENS-111 during the study. The DMC will be regularly provided with safety data. Safety data will be provided by patient with relevant information every 75 patients (around 25 patients/ group) or at least once a year. The first review will be performed after 30 patients have completed the study. The DMC will remain blinded for its evaluation but may ask for un-blinding if required.

Statistical methods:

Sample size calculations: 207 patients (69 patients per group: 20% improvement of the AUC VAS versus placebo, α= 2.5%, β=85%). It is based on the area under the curve (AUC) of the Vertigo Intensity Visual Analog Scale (VI-VAS) from first evaluation after baseline to end of treatment (8 measurements).

The assumptions are the following:

- Each comparison to placebo performed at 2.5% two-sided significance level
- Power of each comparison to placebo set to 85%.
- 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).

Analysis sets:

- The intent-to-treat (ITT) analysis set will comprise all randomized patients according to randomization group. All efficacy analyses will be performed on the ITT analysis set.
- The safety analysis set will comprise all treated patients according to treatment received.

Primary efficacy endpoint:

The VI-VAS AUC will be compared between treatment groups within an analysis of covariance model with the stratification factor (duration of vertigo before being treated) and the baseline score as covariates. The two comparisons to placebo will be tested with an alpha adjusted to the Dunnett's multiple comparison procedure in order to preserve an overall type I error of 5%, the corresponding confidence intervals will be presented.

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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 using a restricted maximum likelihood (REML)-based repeated measures approach. 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 score 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. 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 two comparisons to placebo will be tested at each time using an alpha adjusted according to the Dunnett's multiple comparison procedure in order to preserve an overall type I error of 5% within the time considered and the corresponding confidence intervals will be presented.

Secondary efficacy endpoints:

The baseline and the 8 post-baseline assessments of the Worst VI-VAS will be analyzed using the approach described for the primary endpoint.

The change from baseline of the total score of the Romberg tests at the end of treatment 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 before being treated) and the baseline total score. The two comparisons to placebo will be tested with an alpha adjusted according to the Dunnett's multiple comparison procedure in order to preserve an overall type I error of 5%, the corresponding confidence intervals will be presented. The same approach will be applied to the change from baseline at the end of study.

The change from baseline of the peak slow phase velocity at the end of treatment and the change from baseline at the end of study will be analyzed using the approach described for the total score of the Romberg tests.

The baseline and the 8 post-baseline assessments of the Nausea intensity VAS will be analyzed using the approach described for the primary endpoint.

The change from baseline of the DHI functional sub-score scale at the end of study will be compared between treatment groups within an analysis of covariance model. Patients

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without data available at the end of study will be excluded from the analysis. The two comparisons to placebo will be tested with an alpha adjusted to the Dunnett's multiple comparison procedure in order to preserve an overall type I error of 5%, the corresponding confidence intervals will be presented. The same approach will be applied to the change from baseline of the VADL score at the end of study.

Safety endpoints:

All safety analyses will be performed on the safety analysis set using descriptive statistics.

Adverse events (AEs) will be evaluated for severity and coded using MedDRA. They will be summarized by system organ class and preferred term. Separate summaries of treatment-emergent AEs (TEAEs) will be generated for the following:

- All TEAEs
- Severe TEAEs
- Serious TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs resulting in death

Summary statistics of haematology, blood chemistry and liver function test parameters are presented by treatment group for baseline, post-baseline and change from baseline measurements. Number and percentage of patients presenting at least one post-baseline potentially clinically significant abnormality are presented by treatment group for selected parameters. The same kind of approach is used for vital signs and ECGs.

Study timelines:

Duration of patient's participation: 4 days of treatment and 24 days of follow-up

Urgent safety measures:

In case of voluntary or involuntary overdose, it is recommended to carefully monitor the signs and symptoms. As there is no antidote for SENS-111, intensive care admission should be considered according to clinical status, and the treatment would be the standard one for unspecific drug intoxication, including general support which may include immediate gastric lavage within the first hour after intake to diminish the amount absorbed, continuous monitoring of vital signs, supportive care for cardiovascular function, respiratory aid in case of compromise, electrolyte balance and other measures as clinically indicated.

4 FLOW-CHARTS

		Double-blind Treatment				Follow-up	
Visit	**V1 Screening**	**V2 Inclusion**	**V3**	**V4 End of Hospitalization Visit [4, 5]**	**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	X[6]				X[6]		X
Concomitant medications		X	X	X	X	X	X
Randomization		X					
Efficacy							
Standing vertigo intensity [12]	←----	----------	--------	----------	----------	----------	---------→
Worst vertigo intensity (VAS) [1]		←----------	--------	----------	----------	----------	---------→
Nausea Intensity (VAS)[1]	←----	----------	--------	----------	----------	----------	---------→
Walking assessment[1]		←----------	--------	----------	----------	----------	---------→
Disability Handicap Inventory (DHI)		X					X
VADL							X
Romberg tests[8]		←----	----------	---------→	X		X

		Double-blind Treatment				Follow-up	
Visit	**V1 Screening**	**V2 Inclusion**	**V3**	**V4 End of Hospitalization Visit [4, 5]**	**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)**
VideoOculography (spontaneous nystagmus)		**X**	**X[7]**	**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		**X[10]**			**X**		**X[11]**
Caloric test (optional)		**X[10]**					**X[11]**
Treatment							
Study Drug Intake		**X[2]←----**	**--------**	**----------→[3,4]**			
Compliance			**X**	**X**	**X**		
Safety							
Adverse events	**←-----**	**----------**	**--------**	**----------**	**----------**	**----------**	**----------→**
Pharmacokinetics [9]		**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 given at the site after all assessments have been performed. The second dose will be given 12 hours after (±3 h)
3. The last dose will be given either in the morning or evening of D4 according to the time of first intake.
4. 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.
5. 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.

6. Pregnancy tests will be both urine and blood test, except at end of study visit (urine test only. If the test is positive a blood test will be done for confirmation).
7. Video oculography will be performed daily until the end of hospitalization
8. The Romberg tests will be performed at the inclusion visit prior to the first study drug intake and twice daily in the morning and evening while hospitalized, and at all subsequent onsite visits.
9. 12 hours 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 at H24 and end of treatment visit.
10. Either HIT or caloric test are needed for confirmation of the diagnosis
11. The caloric test and HIT at the end of study visit are optional and part of an ancillary study
12. 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.

5 INTRODUCTION AND RATIONALE

5.1 Acute Unilateral Vestibulopathy

Acute unilateral vestibulopathy (AUV) (previously called acute vestibular neuritis) is the third most frequent cause of peripheral vestibular vertigo, after benign paroxysmal positional vertigo and Menière's disease. It is caused by a sudden unilateral isolated vestibular deficit. The annual incidence is about 3.5 to 15 cases/100,000 according to sparse epidemiological data (3)(17)(18)(21). Onset usually occurs in the mid age. There is no gender difference.

Clinically, AUV is a severe condition, characterized by an acute or subacute onset of severe sustained spinning vertigo associated with nystagmus, postural and gait unsteadiness, nausea and often vomiting. There is no acute hearing loss, tinnitus, and no other neurological symptoms. Patients are unable to cope with their usual daily activities. Most symptoms usually abate spontaneously within several days but they may last one or two weeks. AUV occurs usually once during the life span. It is estimated that about 40% of patients will suffer from sequelae: long term unsteadiness and benign paroxysmal positioning vertigo (15% of patients) (5)(10)(11)(15)(22)(24).

Recovery results from a combination of peripheral restoration of labyrinthine function – usually not complete; contralateral vestibular and somatosensory and visual substitution for the unilateral vestibular deficit and central compensation of the vestibular tone imbalance (2)(33).

The pathophysiology of AUV is unknown. Several hypotheses have been proposed: infection due to the reactivation of a latent Herpes Simplex I infection but also an autoimmune reaction, or acute thrombosis following an acute inflammation (12)(16).

There is no approved therapy for AUV. Many patients are severely impaired by vertigo, nausea and vomiting in the acute phase: these symptoms are major targets for treatment. Nausea and vomiting are usually treated with antihistamins, mostly dimenhydrinate or even benzodiazepines in severe cases (23)(36). However, these treatments induce sedation. Based on theoretical considerations, it has been postulated that they may delay or even reduce central compensation of the vestibular tone imbalance between the two labyrinths, limiting their use to two to three days (3).

The effects of corticosteroids and vestibular exercises (28)(37) are still debated. Shupak et al. (38) showed that corticosteroids might enhance earlier recovery but do not improve long term recovery in contrast to a recent study showing some efficacy on long tem compensation, but not on the acute phase (23).

5.2 Histamine 4 receptor

Histamine is a well-known neurotransmitter and modulator of neural activity in the central and peripheral nervous system such as the peripheral vestibular apparatus.

Histamine is found in central vestibular structures and centrally acting antihistamines modulate symptoms of motion sickness (35) (25) (26).

The histamine H_4 receptor is a G-coupled protein receptor that was initially identified on immune cells, mast cells and eosinophils. Histamine-induced eosinophil and mast cell chemotaxis, and calcium response were shown to be mediated by H_4R. In human mast cells, H_4R mediates the release of leukotrienes, cytokines and chemokines (1) (30).

Recent findings have shown that H_4 receptors are present in the inner ear. They are expressed on peripheral neurons including vestibular neurons (20) (28) (27). The H4 receptor affects primary vestibular neurons (9).

H_4R Knock-Out mice and the administration of H_4R antagonists have demonstrated anti-inflammatory properties in various inflammatory models (8). They were described to modulate vestibular neural activity in ex vivo models and alleviate the induced vestibular deficits in in vivo models.

5.3 SENS-111

SENS-111 is a new highly selective and specific antagonist of the histamine H_4 receptor (H_4R) discovered and initially developed by Palau Pharma (former identification UR-63325). It is developed as a potential novel therapy for patients suffering from AUV with the aim of improving associated symptoms without preventing long tem recovery (see additional information in the Investigator's brochure).

In vitro, SENS-111 binds to human H_4 receptor with high affinity (K_i: 15 nM) and high selectivity, acting as a potent antagonist for this receptor in native cells (IC_{50}: 10 nM). SENS-111 has shown similar binding affinity to H_4 receptor from the main pharmacological and toxicological species, i.e. rat, and monkey, but low affinity for dog H_4 receptor.

5.3.1 Pharmacology studies

The anti-inflammatory effect of SENS-111 was shown in various inflammatory models. Also, preclinical experiments have confirmed the ability of SENS-111 to inhibit vestibular neuron activity (action potential firing) in ex vivo and in vitro tissue preparations.

In rat models of unilateral vestibular lesion, SENS-111 consistently reduced spontaneous nystagmus (measured with videonystagmography VNG) and vestibular deficits (measured with a vestibular behavior rating scale) in a dose-dependent manner after single IV dose (10 to 30 mg/kg).

5.3.2 Preclinical pharmacokinetics

SENS-111 is well absorbed by oral route in mice (F=71%), rats (F=38%) and dogs (F=127%). Protein binding is low. A low extent of metabolism was observed in in-vitro studies. About 50% of SENS-111 is eliminated as unchanged form in urine. Two main metabolites have been observed with a low biliary and urinary excretion. SENS-111 crosses the blood brain barrier in rats and mice with brain/plasma ratios of about 6. SENS-111 reaches the inner ear tissues surrounded by the blood labyrinth barrier with an inner ear/plasma ratio of around 0.3.

Based on non-clinical data in the rat, the target plasma concentrations for vestibular indications in man range between 100 and 300 ng/mL.

In vitro studies have not shown any inhibition or induction of human cytochromes by SENS-111 at expected therapeutic concentrations.

5.4 Non clinical safety pharmacology and toxicology studies

The toxicology of SENS-111 has been studied up to 28 days dosing under GLP conditions. Acute toxicity showed a Minimum Lethal Dose (MLD) after single dosing of 250 mg/kg orally and 50 mg/kg IV in mice, and of 250 mg/kg orally and 70 mg/kg IV in rats.

Oral daily dosing for 28 days to rats and monkeys showed No Observed Adverse Effect Level (NOAEL) of 20 mg/kg/day (C_{max}: 1138 ng/mL AUC_t: 3748 ng•h/mL) in rats, and 12 mg/kg/day (C_{max}: 2148 ng/mL AUC_t: 14890 ng•h/mL) in monkeys, respectively.

Central nervous system (CNS) toxicity was observed at very high doses with SENS-111, notably in the primate; convulsions occurred prior to death at a dose of 80mg/kg (after eight daily doses). Tonic and clonic convulsions were also observed at high doses in mice (50 mg/kg) and rats (70 mg/kg).

A slight depressant CNS effect at the dose of 200 mg/kg was observed at 1 h after administration, in the functional observational battery, a neuro-behavioral assessment test in rats. No other adverse clinical signs suggestive of any CNS toxicity were observed in mice, rats and monkeys.

Repeated dosing up to 28 days in rats and monkeys did not identify any relevant toxicity. SENS-111 was otherwise well tolerated.

Substantial margins (between 27 and 33 fold based upon Cmax) to the no effect dose level give assurance that the proposed dose levels in humans should not induce serious CNS effects in humans following either acute or repeated dosing.

GLP compliant safety pharmacology core battery studies have been performed with SENS-111. No effects on the respiratory function of conscious rats were observed at doses up to 90 mg/kg.

SENS-111 caused elevated heart rate and blood pressure possibly associated with emesis and prolonged QRS complex at the dose of 30 mg/kg ($AUC_{0\text{-}inf}$: 40807 ng•h/mL) in the dog telemetry study. No effect was observed at 10 mg/kg ($AUC_{0\text{-}inf}$: 10272 ng•h/mL). No effects on QTc have been observed.

Additional studies to further characterize any potential CNS and cardiovascular effects included an Irwin test after a single dose and repeated administration, with slight depression effect on the central nervous system after multiple doses of 200 mg/kg, sodium thiopental-induced sleep test in mice and ethanol-induced sleep test in mice, neither of which showed effects at doses up to the highest dose tested. Specific studies in rats and mice to examine the pro-convulsive potential of SENS-111 confirmed high doses to be associated with increased incidence of convulsions but the studies were compromised by lack of an expected effect with the positive controls.

- Finally, SENS-111 inhibited in vitro hERG and Nav1.5 ion channel at very high concentrations (IC_{50} of 242 µM (56,900 ng/mL) and >300 µM (70,000 ng/mL respectively).
- There was no effect on QTc in telemetered beagle dogs at doses up to 30mg/kg, the highest dose evaluated (C_{max}: 6500 ng/mL, AUC0-inf: 40,807 ng•h/mL). Only a slight increase in QRS was observed at 30 mg/kg, which was attributed to one metabolite (UR-67147) present at high concentrations in dogs. There was no in vivo cardiac effect at high concentrations in rats and monkeys.

No target organs and histopathological findings were identified.

So far, fertility or teratology studies have not been conducted. The effect of SENS-111 on pregnancy and newborns is unknown.

SENS-111 is considered to be non-mutagenic according to the standard GLP genotoxic battery that included bacterial reverse mutation, chromosomal aberration test and in vivo micronucleus test.

5.5 Clinical experience with SENS-111

SENS-111 has been tested in 4 clinical studies. Three studies were conducted in healthy subjects as single dose and multiple doses and one study was conducted in subjects with asymptomatic allergic rhinitis otherwise healthy.

SENS-111 has been administered to 172 healthy subjects (men and women not at childbearing potential): 78 received single doses from 2 to 500 mg, and 94 were administered SENS-111 for 4 to 7 days at doses ranging from 5 to 250 mg/day. SENS-111 was well tolerated and the maximal tolerated dose was not reached. The most frequent adverse events were headaches, somnolence and nasopharyngitis observed in both placebo and SENS-111 groups. No dose-dependent adverse event has been observed. There were no cardiac effects.

The pharmacokinetic profile was linear at doses from 5 to 200 mg/day and was slightly over-proportional starting at 250 mg/day. During the single dose part, the highest mean C_{max} and $AUC_{0\text{-}inf}$ were observed at 500 mg (respectively 1135ng/ml and 17419 ng•h/mL). During repeated administration, the highest mean C_{max} was 1088 ng/mL and maximum $AUC_{0\text{-}192}$ was 26,121 ng•h/mL (250 mg/day for 7 days).

$T_{1/2}$ elimination was between 21.8h to 29.9h after single dose and increased with the duration of administration up to 56h after 7 days of SENS-111 250 mg/day.

– Plasma concentrations of the metabolites UR-67147 and UR-64250 were quantifiable at all doses; UR-64167 and UR-64250 exposure respectively amounts to about 5% and 1% of SENS-111 exposure. This percentage did not increase or decrease depending on dose or after a repeated administration. Half-lives were not longer than the parent compound.

5.6 Study Rationale

The proposal to test the efficacy on a H_4 antagonist in the treatment of AUV is based on a scientific rationale:

a) Modulation of vestibular neural activity was shown to be highly effective for treating vertigo of peripheral origin. (Astemizole, a H_1R antagonist not crossing the brain blood barrier).
b) In the inner ear and particularly in the vestibular apparatus, histamine and its metabolites modulate the neural activity through the specific activation of histamine receptors. Such activation can be antagonized by specific histamine- receptors antagonists.
c) Histamine receptors antagonists have shown mild efficacy in peripheral and central vestibular disorders. However their dosage is limited by the induced sedation (e.g., meclizine, dimenhydrinate).
d) Antagonists to H_4R were able to decrease peripheral vestibular imbalance (and thus vertigo symptoms) in animal models,

Based on preclinical data, it is expected that SENS-111 will improve vertigo and associated symptoms of AUV and would reduce the risk of side effects such as sedation with no deleterious effect on central compensation.

In addition, SENS-111 has shown activity on a well-established biomarker model of H_4R antagonism in humans (the histamine-induced eosinophil shape change). In the phase 1 single dose study, SENS-111 was able to reverse the histamine induced eosinophil shape changes at all doses. In the first repeated dose administration study, a dose-dependent effect duration was observed, with a one week activity after 50mg.

A first pharmacology study using cold water-induced nystagmus in healthy subjects did not demonstrate effect on nystagmus at any of the 5 tested doses (50, 100, 150, 200, and 250 mg/day) for 4-7 days. A post-hoc pharmacokinetic/pharmacodynamics evaluation confirmed that SENS-111 was able to delay the onset, and duration of induced vertigo.

5.7 Dose selection

An oral dispersible tablet will be used in this study. Pharmacokinetic parameters confirmed no difference between the ODT and capsules in a dog study.

The dose for this study has been selected from in vitro and in vivo models and from the phase 1 safety studies in human that confirmed the good safety up to 500 mg single dose and 250 mg repeated-dose.

Based on nonclinical data generated in vestibular models in the rat (see Section 5.3.1), the range of targeted plasma concentrations is 100 to 300 ng/mL for a vestibular indication.

Phase I pharmacokinetic data in healthy volunteers showed that these concentrations are achieved at doses between 100 and 200 mg/day repeated doses. The dose of 200 mg/d administered for 7 days resulted in plasma C_{min} (at 24 h post dosing) of 260 ng/mL.

Also, in healthy subjects, the nystagmus-induced test demonstrated the more consistent pharmacodynamic effect at 100-200 mg/day.

SENS-111 100mg and 200mg have been selected for the proposed study. However, it is proposed to start the treatment with 100 or 200 mg administered twice, 12h apart during the first 24 hours to rapidly achieve an active concentration then continue with a once-daily administration for 3 additional days. Pharmacokinetic simulation confirmed that the steady-state is more rapidly achieved with a twice daily (b.i.d.) administration on the first treatment day, and that the C_{max} remains below the highest C_{max}. The duration of treatment was established from the course of the acute vertigo (lasting approximately 1 week) and the half -life of SENS-111.

5.8 Endpoints selection

There are no validated objective tests to assess the efficacy of pharmacotherapy in AUV. Since vertigo is the hallmark symptom of AUV, it has been taken as a marker of the efficacy.

The Vertigo Intensity Visual analog scale (VI-VAS) has been used by several authors to assess vertigo in AUV (34) (31) (32). The scale has been shown to have good test-retest reliability (ICC 0.93–0.96) in subjects with remaining symptoms after AUV. It was confirmed also that the baseline values are correlated with long-term residual symptoms and that the reduction is the greatest during the first week. From a patient perspective, two parameters are important: the severity and the duration of the vertigo; improvement in either is clinically relevant. The AUC of VI-VAS during the first 5 days after the occurrence of AUV is the best way to capture either the severity, the duration or both. Given the natural course of AUV, it is assumed that in the placebo group, the vertigo intensity at the end of treatment will be too small to detect any statistical difference with the active group. For this reason, a rapid decline in vertigo intensity is thought clinically more relevant than low vertigo intensity at the end of the treatment. To account for this dynamic effect, the AUV of the 8 first VAS assessments (including baseline to first evaluation after the last study drug intake) will be used as the primary end-point. In this study the VI-VAS will be evaluated under a standardized condition in each patient to reduce inter-individual variability: standing upright, eyes open, feet close together

The main secondary endpoints will include objective measures of functional impairment (quantified by Romberg tests and a standardized nystagmus evaluation), and measures of disability using two well validated instruments: the DHI (the dizziness handicap inventory) and a more specific to AUV the Vestibular Disorders Activities of Daily Living Scale (VADL) as one of the major consequence of AUV is inability to cope with daily activities, and an objective measure of the ability to walk without support. The later has been shown to directly relate to a physiologic measure of compensation. Also, an additional evaluation of the worst vertigo over the last 2 hours will be also assessed twice daily to account for cyclic variation.

6 STUDY OBJECTIVES AND END-POINTS

6.1 Study Objectives

6.1.1 Primary objective:

To demonstrate the efficacy of SENS-111 in Acute Unilateral Vestibulopathy.

6.1.2 Secondary objectives:

- 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-111in patients with AUV
- To preliminary evaluate the health economics of SENS-111

6.2 Study End points

The study procedures and outcomes are summarized in the flow chart (Section 4) and described in the following paragraphs.

6.2.1 Primary efficacy end point

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

6.2.2 Secondary efficacy endpoints

Comparison between groups of

- Worst spontaneous vertigo intensity measured by the AUC of the worst vertigo visual analogue scale (VI-VAS) over the 4 treatment days (8 post baseline assessments)
- Change from baseline of the total score of the Romberg tests at the end of the treatment (D5) and end of study (D28).
- Peak slow phase velocity of the peripheral vestibular spontaneous nystagmus, measured by oculography in darkness at the end of the treatment (D5) and end of study (D28).
- Nausea severity measured by the AUC of the Nausea Intensity Visual Analogue Scale over the 4 treatment days (8 post baseline assessments)

- The functional disability at the end of study (D28) assessed by the Dizziness Handicap Inventory (DHI) functional subscale score and the Vestibular Disorders Activities of Daily Living Scale (VADL)

6.2.3 Exploratory efficacy endpoints

- Vertigo Intensity in standing position and worst spontaneous at the end of the study (Day 28) assessed by the Vertigo Intensity VAS.
- Time to unassisted walk assessed by a specific question.
- Health economic evaluation assessed with the Work Productivity and Activity Impairment (WPAI-SH) questionnaire at the end of study.

6.2.4 Safety endpoints:

- Adverse events, laboratory, vital signs and ECG

6.2.5 Pharmacokinetics

- SENS-111 pharmacokinetic parameters

7 STUDY DESIGN

7.1 Description of the protocol

This is a double-blind, randomized, 3 parallel-group placebo-controlled, international study. 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 is at least 60mm on a 100mm visual analog scale measured in standing position feet together.

It is planned to enroll 207 patients into the study: 69 patients receiving SENS-111 200mg daily for 4 days, 69 patients receiving SENS-111 100 mg once daily for 4 days, and 69 patients receiving matching placebo (1:1:1 ratio). An additional dose (respectively 200 mg, 100 mg and placebo) will be administered to the patients approximately 12 hours after the first intake.

The screening evaluation including vital signs, a complete oto-neurological examination and nausea and vertigo evaluation will confirm the diagnosis and no exclusion criteria for past medical history, concomitant treatments, laboratory tests or other concomitants diseases. Specific attention will be paid to exclude any patient with a stroke (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 head impulse test or caloric test or both to confirm the diagnosis. They will complete vertigo evaluations with visual analog scales 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.

Patients will be asked to complete a vertigo visual analog scale 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.

24 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 (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.

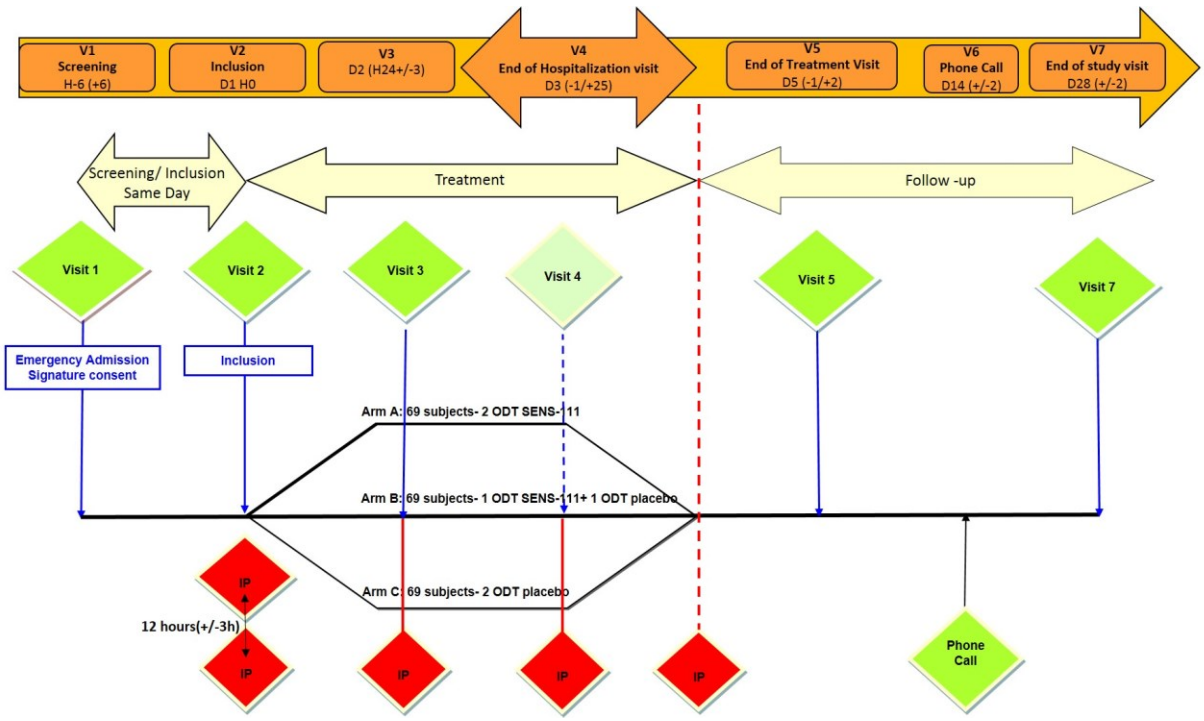
Patients will be followed for adverse events throughout the study. Inquiry about potential adverse events will be done at every on-site visit and on Day 14 when a phone call will be given.

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

A health economic questionnaire will be completed at the end of the study.

At some specific sites, an ancillary test using the VOG will be conducted.

7.2 Study diagram



The inclusion and screening are to be done no more than 24 hours apart.

As soon as eligibility of the patient is confirmed, the investigator will dispense the subject the study drug that is to be taken immediately after all baseline assessments are performed.

7.3 Number of subjects and duration of study participation

It is planned to enroll a total of 207 patients in the study.

The study will be conducted in Europe, US and South Asia and Australia.

Each patient's participation in the study will be 4 weeks:

- 4 days of double blind treatment
- A follow up with no investigational product until 28 Days after inclusion.

7.4 Determination of end of clinical trial (all patients)

The study will be considered complete when all patients have completed all the scheduled procedures as described in the flow chart (Section 4), and all data are captured (database lock). Any withdrawal from treatment during the 4-day treatment period will be considered as treatment discontinuation.

8 INCLUSION AND EXCLUSION CRITERIA

Strict adherence to the inclusion and exclusion criteria is critical to ensure that only patients suffering from AUV are included.

8.1 Inclusion criteria

13. Subjects male or female aged 18 years and above, and below 75 years
14. Suffering from an acute episode of vertigo of peripheral origin defined as follows:
    a. Severe (≥ 60mm on the standing vertigo intensity VAS)
    b. Prolonged (more than 6 hours)
    c. Associated with imbalance and/or postural imbalance, nausea and/or vomiting
    d. Spontaneous nystagmus toward the unaffected ear (fast phase) which is suppressed or reduced by visual fixation confirmed by VOG
    e. Gain of the VOR <0.7 on the video HIT and/or difference between the 2 labyrinths >25% according to the caloric test (de Jongkees' formula).
15. Affiliated or is a beneficiary to a health insurance system (if applicable per national regulations)
16. Having signed and dated written informed consent.

8.2 Exclusion criteria

Patients who have met all the above inclusion criteria listed in Section 8.1 will be screened for the following exclusion criteria:

1. Vertigo duration of less than 6 hours before randomization
2. Acute continuous vertigo lasting more than 72 hours prior to randomization
3. Acute hearing loss during or after the onset of vertigo.
4. Acute unilateral tinnitus during or after the onset of vertigo
5. History of acute or chronic vestibular diseases (Meniere's disease, acute labyrinthitis vestibular migraine..,) vestibular dysfunction, previous episode of acute unilateral vestibulopathy or prolonged vertigo.
6. On-going benign paroxysmal positional vertigo (BPPV)
7. History of prior acute central vestibular lesion.
8. Acute or chronic disease of middle ear (infections, otitis)

9. Concurrent Varicella Zoster Virus ear infection (Herpes zoster oticus)
10. History of cochlear implants
11. Neurological disorders including stroke, brain stem or cerebellar dysfunction within the last 3 months. (In case of possible stroke of the brainstem or cerebellum, the diagnosis should have been excluded by a MRI performed in the past 48 hours)
12. Past or concomitant treatment with ototoxic chemotherapy
13. Past history of seizures or convulsions
14. Head trauma within the last 10 days prior to randomization
15. Aminoglycosides in the past 6 months given via systemic or transtympanic administration
16. Concomitant treatment with any of the followings within the last 24 hours prior to randomization, if more than 2 doses have been taken:
    a. Antihistamines: diphenhydramine, cyclizine, dimenhydrinate, meclizine, hydroxyzine, promethazine,
    b. Cinnarizine, flunarizine
    c. Central anti-dopaminergics: neuroleptics, unless the dose is stable for at least 1 month prior to randomization and no changes are expected during the course of the study
    d. Benzodiazepines
    e. Histaminergics (e.g., betahistine)
    f. Scopolamine, homatropine
    g. Gabapentin, pregabalin
    h. Acetylleucine, 5HT3 antagonists (ondensetron, granisetron, palonosetron etc..)
    i. Piracetam, piribedil, trimetazidine,
    j. Corticosteroids (oral or injectable) unless the dose is stable for at least 1 month prior to randomization and no changes are expected during the course of the study
17. Treatment with any investigational agent within 4 weeks prior to randomization or 5 half-lives of the investigational drug (whichever is longer)
18. Prior participation in a clinical trial with SENS-111
19. History of malignancy other than effectively treated carcinoma in-situ of the cervix, or adequately treated non-metastatic squamous or basal cell carcinoma of the skin, within 5 years
20. Known history of, or concomitant severe hepatic, gastrointestinal, cardiovascular, respiratory, neurological, psychiatric, hematological, renal, or dermatological disease, or any condition, psychiatric, substance abuse, or otherwise, that, in the opinion of the Investigator might interfere with the evaluation of study treatment or warrant exclusion.

21. Pregnancy (a negative pregnancy test is required for all women of childbearing potential before initiation of treatment on Day 1)
22. Male and female patients of child-bearing potential who are unwilling to use an highly effective contraception while enrolled on study and receiving the experimental drug, and for at least 1 month after the last intake of the investigational product. Highly effective therapy includes
    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal or transdermal
    b. Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable or implantable
    c. Intrauterine device (IUD),
    d. Intrauterine hormone-releasing system (IUS)
    e. Bilateral tubal occlusion
    f. Vasectomised partner
    g. Sexual abstinence

    (see complete list in Appendix 11)
23. Nursing mothers
24. Severe abnormal laboratory findings
    k. Creatininemia >1.5 upper limit of normal (ULN))
    l. INR >1.7 ULN, Total bilirubin >2 ULN
    m. ALAT and/or ASAT > 3 x ULN
    n. Hemoglobin <0.9 Giga/L and/or
    o. Neutrophils <1,5 Giga/L and/or
    p. Platelets <100 Giga/L
25. Patients who, in the opinion of the Investigator, have significant medical or psychosocial findings that warrant exclusion. Examples of significant problems include, but are not limited to other serious non-malignancy-associated medical conditions that may be expected to limit life expectancy or significantly increase the risk of SAEs and any condition, psychiatric, substance abuse, or otherwise, that, in the opinion of the Investigator, would preclude informed consent, consistent follow-up, or compliance with any aspect of the study
26. Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.

9 TREATMENT

9.1 Study treatment

SENS-111 100 mg orally disintegrating tablets (ODT), with a matching placebo

dose:

- SENS-111 200mg (100 mg ODT + 100 mg ODT) or
- SENS-111 100mg (100 mg ODT + Placebo ODT) or
- Matching Placebo (2 ODTs)

Given once daily for 4 days.

An additional dose will be given approximately 12 hours (9 to 15 hours) after the first intake. The corresponding total dose will be 1000 mg or 500 mg or 0 mg for the entire study.

Administration Route: The tablet should not be swallowed immediately, nor taken with water. The tablet should be kept in the mouth for a few seconds until dispersion is complete.

There is no food restriction.

9.2 Description of blinding methods

The orally disintegrating placebo tablets match SENS-111 (100 mg) tablets, and are identical. The list of randomization will be generated centrally by Catalent.

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. (see section 12.6 for unblinding method)

9.3 Randomization process

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

A total of 207 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).

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 100mg x 2 ODT, or SENS 100mg 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).

9.4 Packaging and labeling

SENS-111 and matching placebo will be inserted in child resistant aluminium blisters. The blisters are packaged and labeled into a child resistant sealed clinical pack that includes 6 dose regimens (12 tablets) of the investigational product for a 4-day administration and 1 extra day. Each patient will be administered the tablets from the assigned kit. The patient will take the kit at home with the remaining tablets at discharge from the hospital if it occurs prior to the last scheduled intake.

The content of the labeling is in accordance with the local regulatory specifications and requirements.

9.5 Storage conditions

SENS-111 and matching placebo should be stored in a secure location with restricted access to authorized study staff at room temperature as described on the investigational product labeling. The investigational product is under the responsibility of the study site, and should be handled according to local regulations and procedures.

Patients discharged from the investigational site prior to end of treatment visit (D5) should be warned to store the treatment according to the labeling and out of reach of children. They will be requested to return the wallet within the pack with the remaining tablets at the following on site visit (End of treatment visit).

9.6 Drug Accountability

The Investigator is responsible for the accountability of all used and unused study drug. Drug accountability records must be kept current. These records should contain the dates, quantities and identification numbers (or lot numbers) of study drug received by the Investigator, dispensed or administered to specified subjects, returned from subjects (if applicable), disposed of at the site or returned to Sensorion or its designee. These inventories, along with shipment receipts, shipment temperature recordings (if applicable) and storage temperature logs, and IWRS confirmation reports (if applicable), must be made available for inspection by Sensorion's monitoring and QA auditing staff or designees and regulatory agency inspectors. At the conclusion of the study, photocopies of all drug accountability records will be provided to Sensorion.

9.7 Responsibilities

The Investigator, the Hospital Pharmacist, or any other staff member allowed to store and dispense Investigational Product will be responsible for ensuring that the investigational product used in the study is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements.

The investigational product should not be supplied to any non-authorized person, and should not be used other than as described in this protocol.

9.8 Management of treatment at the end of the study

All unused investigational product (IP) will be returned to the designated Clinical Research Organization at the end of the study, as described in the shipment procedure. The site should not destroy any treatment without a specific written information from the sponsor.

In case of destruction of the IP, the information about date and location of destruction, sort and amount of the IP, reason and contact details of the person who destroyed the IP should be recorded.

9.9 Concomitant therapy

9.9.1 Authorized concomitant medication

Any drugs other than those listed below are permitted, if considered necessary for the subject and administered at a stable dose, at the discretion of the Investigator.

Any concomitant medication (started prior to the study and/or prescribed during the study) should be recorded on the case report form. In case of treatment given for any untoward event, an adverse event form should be completed in the CRF.

The highly effective contraception method should be kept unchanged during the study and up to 1 month after the end of the study.

9.9.2 Not permitted concomitant medication

- The medications listed below are not permitted, unless in exceptional circumstances: see below rescue medication
- Antihistamines: diphehydramine, cyclizine, dimenhydrinate, meclizine, hydroxyzine, promethazine
- Cinnarizine, flunarizine
- Central antidopaminergics: Neuroleptics unless the dose is stable for at least 1 month prior to randomization and no changes are expected during the course of the study

- Histaminergics: betahistine
- Scopolamine, homatropine
- Gabapentin, pregabalin
- Acetylleucine, 5HT3 antagonists (ondensetron, granisetron, palonosetron etc..)
- Piracetam, piribedil, trimetazidine
- Non-selective systemic antihistamines (e.g., chlorpheniramine, dexchlorpheniramine, cyproheptadine, diphenhydramine, hydroxyzine, …)
- Corticosteroids, unless the dose is stable for at least 1 month prior to randomization and no changes are expected during the course of the study
- Note: new "generation" antihistamines (cetirizine, loratadine, desloratadine, ebastine, mizolastine, fexofenadine, …) are allowed.

9.9.3 Other prohibited therapy:

No specific vestibular rehabilitation, except the Romberg test, should be performed during the study. Patients will be informed, that staying in bed without stimulating the vestibular organ will prolong central vestibular compensation.

9.9.4 Rescue medication

- In exceptional circumstances, when the patient is presenting with a severe, unbearable vertigo lasting more than 4 days after the first study drug intake, a rescue medication can be given to the patient from Day 5 and onwards: It is recommended to use **non sedative** standard of care therapy, even listed in the above not permitted concomitant medication. The rescue medication (date, dose, indication) should be recorded on the e-CRF.

10 STUDY ASSESSMENTS

10.1 Efficacy assessments

10.1.1 Vertigo intensity visual analog scale (VI-VAS)

The Vertigo Intensity VAS is a non-anchored 100 mm horizontal line. Patients will be asked to rate the intensity of the vertigo placing the cursor of the electronic device on the 100 mm line to indicate the severity from 0 – 100 when 0 indicates no severity and 100 indicates worst severity. Patients will be requested to rate their vertigo at screening for inclusion criterion, just before the first study drug intake for baseline, and then twice daily in the morning between 10am and 12pm and in the evening just after dinner up to the end of study. An electronic device will be given to the patient for rating. The date and exact time of the rating will be captured together with the intensity.

Two conditions will be tested:

- **Standing vertigo intensity** (see Appendix 1): Patients will be asked to rate the intensity of the vertigo while standing up, eyes open, feet together twice daily. The vertigo assessment will be performed under condition 1 of the Romberg test on site to make sure that there is no risk of falling. When the patient is at home, he will be asked to try to stand up, to rate the standing vertigo intensity. He/she should be warned against the unability to stand up without support and the risk of falling. The patient should be recommended to try to stand up, close to his/her bed, to get support if needed, and if possible with someone close by to prevent any fall.
- **Spontaneous worst vertigo** (See Appendix 2): Patients will be asked to rate the worst intensity of the vertigo over the last 2 hours, if possible prior to the Romberg tests or to the standing vertigo

At baseline, and on site visits if the subject is unable to rate the vertigo due to severity of nausea and/or vertigo, or inability to stand up, the VAS will be verbally assessed (0 to 100), the reason for the patient not rating and the rating will be captured in the eCRF.

At time points other than baseline, in case the patient is unable to complete the test, the reason should be reported within 24 hours (eg: Severe vertigo, Severe nausea, other) on the electronic device.

10.1.2 Nausea Intensity Visual analog scale

The nausea Intensity Visual analog scale is a non-anchored 100 mm horizontal line. Patients will be asked to rate the worst intensity of their nausea over the past 2 hours placing the cursor of the electronic device on the 100 mm line to indicate the severity from 0 – 100 when 0 indicates no severity and 100 indicates worse severity (see Appendix 3).

The nausea intensity will be rated just before the first study drug intake, and then twice daily in the morning and in the evening up to the end of study. An electronic device will be given to the patient for rating. The date and exact time of the rating will be captured together with the intensity.

10.1.3 The Dizziness Handicap Inventory (DHI)

DHI is widely used to evaluate self-perceived handicap due to dizziness, and is known to correlate with vestibular function tests in chronic dizziness (13) (29). First described by Jacobsen and Newman, the original DHI comprises 25 questions designed to assess the patient's disability displayed by functional (DHI-F) (9 questions), emotional (9 questions) and physical (7 questions) limitations. The patient is asked to answer each question using "yes" (4 points), "sometimes" (2 points) and "no" (0 points) (See Appendix 4). The functional aspects investigated by the DHI-F evaluate the interference of dizziness on the performance of some eye, head and body movements, although focusing on the capacity of performing professional, domestic, social and pleasure activities and on the independency of performing tasks such as walking without help and walking around the house in the dark. The score of the functional disability subscale ranges from 0 suggesting the absence of any functional handicap to 36 points indicating the worst functional disturbance.

The DHI has been reported to have good psychometric properties: high test-retest reliability (interclass correlation coefficient [ICC] 0.72-0.97) and internal consistency reliability (Cronbach α = 0.72- 0.89) responsiveness.

In case the patient is unable to complete the test, the investigator will complete the e CRF with the reason of missing data (eg: Severe vertigo, Severe nausea, other).

Patients will be requested to complete the DHI at baseline (prior to the first study drug intake), and end of study visit (D28). Comparison in the functional subscore will be considered.

10.1.4 Time to unassisted walking

Patient will have to express their ability to walk without assistance on the electronic device (see 0). They will have to tick a box "yes" or "no" corresponding to their response to the following 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?"* Walking as usual without support will be considered at the first time when the patient is ticking "yes" and all further assessments are "yes".

10.1.5 The Vestibular Disorders Activities of Daily Living

The Vestibular Disorders Activities of Daily Living scale (VADL) (see Appendix 5) (39) assesses the impact of vestibular impairment on every day activities. The test evaluates self-perceived functional limitations regardless of the underlying pathophysiology. Functional performance was shown to directly relate to a physiologic measure of compensation (40). It includes 28 items grouped into three dimensions: functional (self-care and intimate activities), ambulation (walking and stair climbing), and instrumental (home management and leisure activities).Each item is scored from 1 to 11. 1 to rate for independent, to 10 (too difficult, no longer performed). Rating 11 corresponds to not applicable. This scale has been recently validated in a population of Acute Unilateral vestibulopathy. It will be performed only at the end of study visit.

10.1.6 Videooculography (VOG):

Eye movements will be recorded using a standardized portable videooculography (VOG). Usually, AUV cause a jerk nystagmus with linear or constant velocity slow phase drifts. Characteristically, the nystagmus increases when the eyes are turned in the direction of the fast phases (opposite to the side of the lesion), and can be markedly suppressed by visual fixation. A change in head position often exacerbates the nystagmus.

The experiment is a non-invasive, video-based method to measure the fast and slow phase of the nystagmus. It is based on pupil tracking through infrared cameras. Patients will be in complete darkness for the experiment (see Appendix 8).

The nystagmus intensity defined as the slow-phase velocity (SPV) will be recorded. The SPV is automatically calculated by the apparatus. It corresponds to the distance that the eye travels during the slow phase divided by the duration (SPV = $\Delta\Theta/\Delta t$). Several eye movements are analyzed to calculate the maximum SPV: the nystagmus beat with the highest speed as reported during the experiment.

The test will be performed at baseline (prior to the first study drug intake for inclusion), and daily until the end of hospitalization visit and at the end of treatment visit (D5) and End of study visit (D28).

In case the patient is unable to complete the test, the investigator will complete the eCRF with the reason of missing data (eg: Severe vertigo, Severe nausea, other).

10.1.7 The Romberg tests

The modified Romberg test of Standing Balance was described by Agrawal Y and al. in 2011 (4). It is a static balance testing the patient's ability to stand unassisted under several test conditions with the eyes successively open and closed. This test specifically evaluates the sensory inputs that contribute to balance: the vestibular system, vision, and proprioception.

In order to assess the potential risk of falls and imbalance related to vestibular function, a derived procedure of the modified Romberg test of Standing Balance is proposed (see Appendix 10) The patient is asked to stand, shoes off, in six successive conditions of increasing difficulties, eyes open, and eyes closed, feet together on a firm then foam surface or in tandem position.

Condition 1: Standing on the floor, feet together (or at a distance for them to be steady) with the eyes open looking straight ahead

Condition 2: Standing on the floor, feet together (or at a distance for them to be steady) with the eyes closed

Condition 3: Standing on a foam pad, feet together (or at a distance for them to be steady) with the eyes open looking straight ahead

Condition 4: Standing on a foam pad, feet together (or at a distance for them to be steady) with the eyes closed

Condition 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)

Condition 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).

Importantly, after condition 1, the patient will be requested to fill in the standing vertigo intensity VAS on his/her electronic device.

Each condition is scored as a success or a failure; the failure being defined as one of the following:

- The subject cannot stand up, and is unable to do the test or
- Any occurrence of any of the following within 5 seconds:
    - Movement of the subject's feet from the initial test position (falling, side-stepping, hopping, pivoting, etc.);
    - Eyes open during an eyes-closed condition (i.e., Conditions 2, 4 and 6);
    - Requirement of the operator intervention to prevent the subject from falling or to maintain balance.

The Romberg test will be repeated twice daily during hospitalization and will be performed at every on site visits. The total score will be calculated by summing the rate of each condition with 1 as a success and 0 as a failure. Subscores will be calculated for eyes closed on one hand and eyes open on the other hand

10.1.8 The caloric test

This test is usually performed with the subject reclining, head inclined 30° up from horizontal so as to make the lateral canal horizontal. Water is introduced into the ear canal on one side, either 7°C above

or below assumed body temperature. The flow rate is such that the ear rapidly equilibrates with the water. The water is stopped after 20 seconds, and nystagmus is observed. Nystagmus commonly builds for about 30 – 60 seconds, then gradually decays away over roughly 2 minutes. After a rest of at least 2 minutes, the procedure is repeated with either the opposite temperature water, or on the other side.

Eye movements are usually recorded with either electronystagmography or video.

From the peak slow-phase velocity of nystagmus four numbers are obtained

- cold right : RC
- cold left : LC
- warm right : RW
- warm left : LW

Spontaneous nystagmus should be subtracted from these, and then the absolute value taken. From these responses, LC, LW, RC, RW, three additional numbers are derived: The total response is the absolute sum of all appropriately directed responses. TR= (RC+LC+RW+LW). The goal is to detect bilateral weakness. The total response should be 20 or greater. When responses are corrected for spontaneous nystagmus, the procedure here is to sum the absolute value of responses that go in the right direction - i.e. left cold and right warm should be right-beating, right cold and left warm should be left beating.

Unilateral paresis or RVR (relative vestibular reduction), RVR = (RC+RW-LC+LW)/TR is called "de Jongkees' formula". If all responses are appropriately directed, one can simply take the sum of the absolute values of responses due to the right ear, subtract the sum of the absolute responses due to the left, and normalize to the sum of the absolute values of all responses. If spontaneous nystagmus is not subtracted off first, peculiar results may appear, such as greater than 100% paresis (which is obviously impossible).

The test can be performed at baseline for inclusion if the vHIT is negative and all other criteria are met. The RVR should be > 25% (de Jongkees' formula).

Caloric tests at baseline and end of study visit will be performed in some centers participating in an ancillary study.

10.1.9 The video Head Impulse Test

The video Head Impulse Test (vHIT) (see Appendix 9) provides a quick and objective measure of the vestibular ocular reflex (VOR) in response to head movements in the natural range of daily motions. AUV patients are reported to have reduced horizontal canal VOR gain (6)(7).

vHIT is an easy tool to determine corrective saccades (overt and covert) in patients, when delivering manually graded head impulses and to objectively analyze the stimulus-response characteristics of the VOR.

This procedure provides the clinician with a video recording of eye movement for spontaneous, dynamic positional and positioning maneuvers. It also allows a "bedside" type of neurovestibular evaluation of

the patient's ability to hold gaze and the presence or absence of nystagmus in the aforementioned subtests.

Eye movements are recorded via VOG goggles to quantify eye and head movements and to calculate gain as a ratio of angular eye velocity to angular head velocity. The vHIT will be conducted at baseline to confirm the peripheral origin of the vertigo. AUV is confirmed if the VOR gain is <0.7 or if there is a pathological caloric testing and all other criteria are met. (see Appendix 8)

An additional vHIT will be performed at the end of treatment and end of study visits in some centers participating in the ancillary study.

10.2 Safety assessments

Clinical safety will be routinely assessed by the medically-qualified study investigator.

10.2.1 Physical examination

A physical examination including evaluation of main body systems/regions: skin and mucous, ears/nose/throat, pulmonary, cardiac, gastro-intestinal and neurological systems is to be conducted at the Screening visit, on Day 5 (Visit 5, EOT), and Day 28 (Visit 7, EOS). Care should be taken to examine and assess any abnormalities that have been indicated as potentially present by medical history.

10.2.2 Vital signs

Vital signs including temperature, systolic (SBP) and diastolic (DBP) blood pressures, heart rate, and respiration will be collected after 10 minutes rest in the supine and after 2 minutes in the standing position. Orthostatic blood pressure is part of the symptomatology described in patients with AUV. If possible, vital signs will be measured prior to blood draw.

Vital signs and orthostatic hypotension will be measured at screening, at baseline (prior to the first study drug intake, 12 and 24 hours after the first intake, at the end of treatment visit (D5) and End of study visit (D28).

10.2.3 Electrocardiogram (ECG)

A standard 12-lead electrocardiogram (ECG) will be performed at the Screening visit, on Day 5 (visit 5, EOT), and Day 28 (Visit 7, EOS). Heart rate will be recorded from the ventricular rate and the PR, QRS and QTc (QTc=QT/[60/heart rate]1/2) intervals will be recorded. The Investigator medical opinion and automatic values will be recorded in the eCRF .The ECG strips or reports will be stored as source document.

10.2.4 Laboratory safety

A standard laboratory blood test will be performed at the screening visit and at D5 (visit 5 EOT visit). Routine serum hematology and chemistry samples will be collected in EDTA tubes and according to the study flow chart and kept at the local laboratory as per laboratory requirements

The standard laboratory blood test comprises:

- hematology : complete blood count (CBC), including hematocrit, hemoglobin, red blood cell count, white blood cell count with differential count,platelets, and INR
- serum chemistry including: sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, albumin, lactate dehydrogenase (LDH), alanine amino transferase (ALT), aspartate serine transferase (AST), alkaline phosphatase, GGT and total bilirubin, fasting glycaemia (at screening glycaemia will not be necessarily fasting), creatine phosphokinase(CPK).
- C Reactive Protein (CRP).
- βHCG will be performed in women of childbearing potential at screening, and at the end of treatment visit, with a urine pregnancy test performed at the screening visit. A subject cannot be included with a positive urine test. Blood sample will be taken for confirmation of the pregnancy status at baseline and end of study visit. In case of positive results, the pregnancy outcome should be reported on a specific form.

No centralized laboratory procedure is planned.. Biological samples will be analysed locally and destroyed immediately after the analyses.

10.2.5 Adverse event collection

Adverse events will be collected throughout the study and at every visit after screening. The medically-qualified investigator will be available to provide clinical judgment on all trial-related medical issues including adverse events and clinical laboratory values.

10.3 Pharmacokinetic evaluation

Serum samples will be collected for pharmacokinetic (PK) analysis. A 3 mL blood sample will be drawn into a Vacutainer tube, at H12, H24, and at end of treatment visit. The blood samples must be gently inverted a few times for complete mixing with the anticoagulant (lithium heparin). The exact date and time of sample collection will be recorded on the eCRF. Within 30 minutes following blood collection, each blood sample will be centrifuged at 1500 *g* for 10 minutes at 4°C.

Samples will be stored at the site in a secure location at -20°C as per laboratory requirements and outlined in the laboratory manual which will be available at each investigational site, until shipment in dry ice to Atlanbio (Saint-Nazaire, France) that will perform the pharmacokinetic analyses.

Several samples will be batched together in the same shipment. The person in charge of the shipment will be contacted by the CRO who will organize samples' shipment. If the site needs to transfer the samples rapidly (due to storage constraint for instance), the CRO should be contacted.

PK samples will be destroyed after the finalization of the complete Clinical Study Report. No further uses of biological samples are planned, i.e for additional research.

10.4 Health Economic:

Health impairment often leads to work impairment in the form of both absenteeism and presenteeism (i.e. reduced productivity while at work). The Work Productivity and Activity Impairment (WPAI-SH) questionnaire (see Appendix 6) is a well-validated instrument (19) that measures impairments in work and activities over the past 7 days. It is the most frequently used instrument.

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

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

11 STUDY PROCEDURES

11.1 Visit

Study procedures are described in the flow chart (Section 4)) The following are general guidance relating to all visits.

Every attempt should be made to complete all visits during the defined window periods.

An end of study visit is required for all patients. In the rare cases a final follow-up visit cannot occur within the 30-day timeframe following the scheduled study end date, any attempt to contact should be recorded on a special contact form, until/unless appropriate information is obtained which will allow completion of final end of study visit CRF, even after the anticipated timeframe.

Blood is collected by venipuncture. The exact time of sample collection should be transferred into database and should be collected on the laboratory request form for local blood sampling.

Important note: Any abnormal laboratory value, abnormal ECG parameter, SAE will be immediately rechecked for confirmation before making a decision of permanent discontinuation of IP for the corresponding patient.

- Patient will be provided with an electronic device for assessment of the VAS during the study. The use of the device will be explained to the patient by the investigator's team and tested prior to the first use.
- Patient may not be able to complete all tests due to the severity of the vertigo. In case of missing data, the reason should be specified in the eCRF (severe vertigo, severe nausea, or other) or in the electronic device if the patient is already discharged.

11.1.1 Visit 1 - Screening H-6 (± 6)

Before any screening assessment is performed, complete and detailed information about the aim, the consequences and the constraints of the trial will be given by a physician, both verbally and by reviewing the information leaflet and consent form. If the subject agrees to perform the study, he will sign and date the Informed Consent form prior to any study-specific procedure. He will be given a copy of the information leaflet and consent form.

After obtaining consent, the investigator will connect to the site http://www.prgrand.com secured by an SSL certificate to create the patient in the database data (patient attribution of code).

The following tests and procedures will be performed:

- Assessment of eligibility by review of inclusion and exclusion criteria
- Recording of the subject demography
- Complete Physical examination: Special attention should be paid to dizziness, migraine, nausea, vomiting (start and duration)

- Previous Medical and surgical history including neurological and psychiatric history
- Neuro-Otologic examination
- Concomitant medications (over the past 3 months). Specific attention will be paid to medication and doses that might have been taken during transportation.
- Vital signs: supine blood pressure and heart rate, Temperature
- Blood collection for routine hematology
- Blood collection for serum chemistry
- C Reactive Protein (CRP).
- Urinary Pregnancy test: both and blood (for WOCBP)
- Standing Vertigo intensity (VAS)
- Nausea intensity (VAS)

11.1.2 Visit 2 - Inclusion H0

If the patient meets all inclusion and no exclusion criteria (per history, exam and laboratory) the patient can be included in the study.

The following tests and procedures will be performed:

- Re-Confirmation of medical history (dizziness, migraine, nausea, vomiting (start and duration)
- Vital signs: supine and standing blood pressure and heart rate, Temperature
- 12-lead ECG
- Checking for Concomitant medication and doses of unauthorized medication;
- Re-confirmation of eligibility by reviewing inclusion/exclusion criteria
- Inquiring about adverse event and fill an adverse event form if any
- The patient will be provided with an electronic device. He will be instructed to fill in the worst vertigo intensity VAS and the nausea intensity VAS, and to answer to unassisted walking ability question.
- The patient will be asked to complete specific tests
    - Romberg tests with a standing vertigo intensity VAS under condition 1.
    - Videooculography
    - Video Head Impulse test and/ or Caloric test
    - DHI
- Recording of the Hospitalization status of the patient (yes/no)
- After all assessments have been completed, the investigator will connect to the IWRS for allocation of a randomized treatment kit number. The investigator will dispense to the subject the corresponding study drug that is to be taken at the site, immediately after all baseline assessments are performed. Patient should be instructed to take 2 tablets and to keep the tablets

in the mouth until complete dispersion. Date and time of the intake should be recorded on the e-CRF.

- The patient remains under medical supervisions for at least six hours after the study drug intake.

11.1.3 Visit 2 - H12 (± 3hours)

- Patient will be instructed to continue to fill in the worst vertigo intensity VAS and the nausea intensity VAS, and answer to the walking ability question twice daily in the morning between 10.00 am and 12.00 pm and in the evening just after dinner.
- Inquiring about adverse event and fill an adverse event form if any
- The investigator will dispense the second dose of the investigational product, 12 hours (±3 h) after the first intake, if there is no adverse event leading to discontinuation, and after
    - Vital signs are assessed and
    - a blood sample taken for PK
    - Romberg tests are performed with the standing vertigo VAS to complete under condition 1.

Date and time of the intake should be recorded on the e-CRF.

11.1.4 Visit 3 - H24 (± 3hours)

The following tests and procedures will be performed:

- Checking for Concomitant medication
- Inquiring about adverse event and fill an adverse event form if any
- Vital signs: supine and standing blood pressure and heart rate, Temperature
- The electronic device information for VAS completion will be checked
- Patient will be asked to complete specific tests

    - The Romberg tests that will be repeated twice daily until the patient is discharged with the standing vertigo intensity VAS just after condition 1.
    - Videooculography

- Hospitalization status (Yes/No)
- Drug accountability
- A blood sample will be taken for PK.
- Patient will be instructed to take the third dose of the investigational product and to continue once daily for the fourth, and the fifth doses in the morning or evening depending on the time of the first intake.
- Patient will be reminded to fill in the Vertigo intensity VAS and the nausea intensity VAS on the electronic device and to answer to the unassisted walking ability question twice daily in the morning between 10.00 am and 12.00pm and in the evening just after dinner.

- If the patient is discharged, he will be instructed to record also a standing vertigo intensity VAS while standing on a firm surface, eyes open, feet together.
- An appointment for Visit 5 D5 (end of treatment visit) will be scheduled.

11.1.5 Visit 4: End of hospitalization visit, From D3 (-1, +25) to D28

The discharge visit has to be done the day of discharge from the hospital. If it occurs on D5 (-1; +2) (end of treatment visit) or on Day 28 (±2) (end of study visit), only the information about date and time of hospital discharge will be captured in the e CRF.

The following tests and procedures will be performed:

- Checking for Concomitant medication
- Inquiring about adverse event and fill an adverse event form if any
- Vital signs: supine and standing blood pressure and heart rate, Temperature
- The electronic device information for VAS completion will be checked
- Patient will be asked to complete specific tests
    - The Romberg tests with a standing vertigo intensity VAS after condition 1
    - Videooculography
- He will be requested to return the device to the site at the following visit.
- Hospitalization status (Yes/No)
- Drug accountability
- If the discharge visit occurs prior to Day 5, Patient will be provided with the treatment kit with the remaining tablets to be taken home. He will be instructed to take 2 tablets in the morning or evening depending on the time of the first intake the last intake being on D4 (if relevant).
- Patient will be provided with the electronic device to be taken home and he will be reminded to fill in the worst vertigo intensity VAS and the nausea intensity VAS, as well as to answer to the unassisted walking ability question twice daily in the morning between 10am and 12pm and in the evening just after dinner. He will be instructed to record also a standing vertigo intensity VAS while standing on a firm surface, eyes open, feet together twice daily.
- If the patient is still at the study site (hospital) at the time of end of study visit, or if the end of hospitalization visit is within the window of the end of treatment visit, the end of hospitalization visit will not be completed and the reason clearly mentioned in the e CRF. .
- An appointment for the following visit will be scheduled, and the patient will be instructed to bring the investigational product kit with the remaining tablets together with the electronic device, and to come in fasting condition.

11.1.6 Visit 5: End of treatment visit: D5 (-1/+2 days)

This visit includes:

- Checking for Concomitant medication
- Inquiring about adverse event and fill an adverse event form if any
- Physical examination including the body weight
- Vital signs: supine and standing blood pressure and heart rate, Temperature
- 12-lead ECG
- Drug accountability
- A blood sample will be taken for PK.
- Routine hematology
- Routine biochemistry
- C Reactive Protein (CRP)
- Pregnancy tests both urinary and blood for WOCBP
- The patient will be asked to complete specific tests:
- The Romberg tests with a standing vertigo intensity VAS after condition 1
- Videooculography
- Recording of the Hospitalization status of the patient (yes/no)
- The electronic device information for VAS and unassisted walking ability question completion will be checked
- Patient will be reminded to fill in the Vertigo intensity VAS and the nausea intensity VAS as well as to answer to the walking ability question twice daily in the morning between 10am and 12pm and in the evening just after dinner. He will be instructed to record also a standing vertigo intensity VAS while standing on a firm surface, eyes open, feet together twice daily.
- He will be requested to return the device to the site at the following visit.
- Appointment to the following visits will be scheduled (end of study visit at the site, and phone call).
- Ancillary study: An additional test may be performed at sites participating in the ancillary study: Video-head impulse test (function of the vestibule-ocular reflex)

11.1.7 Visit 6: Phone Call; D14 (±2 days)

A call will be given to ensure safety of the patient. The visit can be performed by phone if the patient is no longer hospitalized. It will include:

- Checking for Concomitant medication
- Inquiring about adverse event and fill an adverse event form if any; In case an event is identified during the phone call, a subsequent visit at the site may be required in order to allow appropriate documentation of the safety event.

- The patient will be reminded to complete the VAS and unassisted walking ability question twice daily in the morning between 10am and 12pm and in the evening just after dinner. He will be also reminded to record also a standing vertigo intensity VAS while standing on a firm surface, eyes open, feet together twice daily.
- Recording of the Hospitalization status
- Appointment to the following visit will be reminded (end of study visit at the site, and phone call), and the patient will be reminded to return the electronic device back to the site, and to be in fasting condition for the V7.

11.1.8 Visit 7: End of study visit; Day 28 (±2 days):

This visit includes:

- Checking for Concomitant medication
- Inquiring about adverse event and fill an adverse event form if any
- Physical examination
- Vital signs: supine and standing blood pressure and heart rate, Temperature
- Drug accountability (if relevant)
- Urinary Pregnancy tests for WOCBP (In case of positive test, a blood sample will be taken for confirmation)
- The patient will be asked to complete specific questionnaires and tests :
    - VADL
    - DHI
    - The Romberg tests with a standing vertigo intensity VAS after condition 1
    - Videooculography
    - Health economic questionnaire: WPAI
- Recording of the Hospitalization status of the patient (yes/no)
- The electronic device information for VAS completion will be checked, and the device stored at the site

Ancillary study: An additional test will be performed at sites participating in the ancillary study

- Video-head impulse test (function of the vestibule-ocular reflex) and/or a caloric test

11.1.9 Unscheduled Visit: Visit 99

In case of adverse event, or in case of abnormal values, an additional visit may be needed to repeat the test or document an adverse event.

11.2 Definition of source data

The list of information considered to be raw data which must be shown in the subject's file are listed in the section 19.

The results of certain investigations or assessments included in the CRF may be considered to be raw data. Direct CRF data entries, if any, should be defined during initiation visits at the latest, by the investigational team and implemented for the rest of the study.

11.3 Subject withdrawal

11.3.1 Removal of subjects from therapy or assessment

In accordance with the current revision of the Declaration of Helsinki and current US Food and Drug law, a subject has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The Investigator and Sponsor also have the right to withdraw subjects from the study in the event of intercurrent illness, adverse events, treatment failure, protocol violation, or other reasons. Should a subject (or a subject's legally authorized representative) decide to withdraw, all efforts will be made to follow the patient and to complete and report the observations as thoroughly as possible on the appropriate case report form.

Subjects who discontinue treatment should be assessed in accordance with the assessments/tests specified normally for the end of study visit.

Subjects who have been withdrawn from the study cannot be re-included in the study. Their subject number and treatment number must not be re-used. They should not be replaced.

11.3.2 Withdrawal criteria

The subjects could withdraw from the study if they decided to do so, at any time and irrespective of the reason, or this could be the Investigator's decision. All drops out must be documented and the investigator must give the reason (adverse event, subject request, other reason…).

Subjects may be removed from the study by the investigator or the sponsor, if one or more of the following occurs:

- Noncompliance with protocol by the subject.
- Adverse event (decision to be removed from study made by either the Investigator or subject). All adverse events, both serious and non-serious, that result in the subject's withdrawal from the study (either by subject request or Investigator decision) must be reported to the CRO (Sensorion designee) within 24 hours for serious events, and within 7 days for non-serious events.

- Worsening of the disease :
    - Worsening of nausea of more than 20 mm compared to baseline on the nausea intensity VAS on 2 consecutive evaluations
    - Worsening of vertigo of more than 20 mm compared to baseline on the VI-VAS scale standing position on 2 consecutive evaluations

  Any worsening is considered an adverse event and must be reported to the CRO (Sensorion designee) within 24 hours for serious events, and within 7 days for non-serious events.
- Onset of new neurological symptoms (such as but not limited to diplopia, slurred speech, gait disturbances, localised weakness or numbness)
- Hearing Loss.
- Positive serum pregnancy test
- Decision by the Investigator or Sponsor that termination is in the subject's best medical interest or administrative decision for a reason other than that of an adverse event.
- Request for withdrawal by the subject for reasons other than an intolerable adverse event.
- Lost to follow-up: For subjects considered lost to follow-up, the CRF must be filled in up to the last visit performed. The Investigator should make every effort to re-contact and to identify the reason why the subject failed to attend the visit and to determine his/her health status.

11.3.3 Decided by the sponsor

The Sponsor could decide premature discontinuation of the study in the following cases:

- The study was not conducted in accordance with the procedures defined in the approved protocol (i.e. low rate of recruiting - protocol deviations - failure to ensure the quality of the data collected).
- Information on the Investigational Medicinal Product (IMP) that could change the current benefit-risk profile of the IMP or that would be sufficient to require changes in the IMP administration or in the overall conduct of the trial.
- Left at the discretion of the Sponsor.

11.3.4 Decided by the investigator

The Investigator could stop the research if in his judgment the participating subjects were exposed to risks that were not ethically or scientifically justifiable and must notify in writing the Sponsor of this decision providing the reason thereof.

In all cases IRBs and Health Authorities should be informed by sponsor, within 15 days after the decision was taken.

12 SAFETY

12.1 Definitions

12.1.1 Adverse event (AE)

An AE is any untoward medical event in a patient or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

12.1.2 Serious adverse event (SAE)

A Serious AE is any untoward medical occurrence that at any dose:

- Results in death - Includes all deaths, even those that appear to be completely unrelated to study drug (e.g., car accident where subject is a passenger).
- Is life-threatening - In the view of the Investigator, the subject is at immediate risk of death at the time of the event. This does not include an AE that had if occurred in a more severe form, might have caused death.
- Requires in-patient hospitalization or prolongation of existing hospitalization. Prolongation of existing hospitalization is defined as hospital stay longer than originally anticipated for the event or development of a new AE as determined by the Investigator or treating physician.
- Results in persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other serious outcomes listed above (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

12.1.3 Unexpected adverse reaction

An unexpected adverse reaction is an adverse reaction, whose nature, severity or outcome is not consistent with the applicable medicinal product information i.e. the Investigator's Brochure.

The occurrence of a pregnancy of a partner of a trial subject discovered within 10 days after last administration of the IMP, is to be communicated to the Sponsor in an expedited manner with the same procedure and timelines as for serious adverse events, independently from the occurrence of an AE.

12.2 Overdose

In case of voluntary or involuntary overdose, it is recommended to carefully monitor the signs and symptoms. As there is no antidote for SENS-111, intensive care admission should be considered according to clinical status, and the treatment would be the standard one for unspecific drug intoxication, including general support which may include immediate gastric lavage within the first hour after intake to diminish the amount absorbed, continuous monitoring of vital signs, supportive care for cardiovascular function, respiratory aid in case of compromise, electrolyte balance and other measures as clinically indicated.

12.3 Reporting of adverse events

12.3.1 Adverse events

Any AE occurring after the patient has signed the informed consent must be fully recorded in the patient's eCRF. The AE form should be supported by a complete documentation available in the patient's file. Any abnormal laboratory test considered medically meaningful (e.g., causing the patient to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged medically relevant by the investigator) should be reported as an AE. The AE should be fully described along with start and stop dates, severity, relationship to the investigational product, action taken and outcome in the AE form.

For any adverse event, the investigator has to follow-up the case to determine the outcome of the adverse event. He should also try to get all necessary information to assess whether the AE meets the criterion definition of a non-serious or a serious adverse event (SAE). In the later case, it will trigger immediate notification to the Sponsor (see below). Whichever the seriousness criterion, follow-up of the AE is requested until final outcome in case of ongoing adverse event or ongoing complication even after the treatment is discontinued.

Final outcome includes complete resolution or stabilization at a level acceptable to the investigator and the Sponsor. For subjects withdrawn from the study and subjects experiencing AE at the end of the study and within 30 days following the last treatment day, the investigator will manage the appropriate follow up (if required until the AEs are resolved or attributed to a cause other than the study drug).

12.3.2 Serious adverse events

SAEs or suspected adverse event must be reported on the specific SAE form. This SAE form must be completed and forwarded to the designated CRO immediately and no later than 24 hours of learning of the event.

The Sponsor will ensure that all legal reporting requirements are met.

The initial report must be as complete as possible, including all details of the current illness and (serious) AE, and an assessment of the causal relationship between the event and the study

medication.

The serious adverse event or medically important event should be fully documented. All additional information not available at the time of the initial report (e.g., AE end, date laboratory values received after the report) must be reported on a follow-up SAE form and transmitted to the designated CRO as soon as possible.

Whatever relationship to the study drug any serious adverse event occurring within **30** days following the last treatment day must be reported.

Contact details for SAE reporting to the designated CRO are the following:

For US sites:

fax [redacted] OR e-mail **GlobalPV-US@[redacted].com**

For all other countries sites:

Fax [redacted] OR e-mail **PVDS-ROW@[redacted].com**

An inquiry will then be conducted by the designated CRO in order to determine whether the event was caused by the treatment to make all necessary submission. In any case, and as a conservative measure, Sensorion will re-assess only cases that were considered not related to the study drug by the investigator.

Sensorion (or designated CRO) will inform the Health Authorities and the Ethics Committees in writing in accordance with current regulations.

12.3.3 Severity and causality of events

The Investigator should assess any event with regard to its severity and causality.

The severity of the adverse events is determined in the following manner:

- mild: no interference with the subject's daily activities
- moderate: moderate interference with the subject's daily activities
- severe: major and unacceptable interference with the subject's daily activities

Both the investigator and the sponsor will assess the possible relationship between the adverse event and the study drug:

- Probable: assuming a causal relationship;
- Possible: a causal relationship cannot be excluded
- Unlikely: a causal relationship with another origin is more likely Unrelated;

- Not assessable: impossible to assess, because of insufficient evidence, conflicting data or poor documentation.

Any adverse event for which, either the Investigator or the Sponsor considers that a causal link with the study product could reasonably be envisaged, is considered a suspected adverse effects. Both the Sponsor and the Investigator's assessment with regard to causality will be reported in the declaration of suspected adverse effect. In no case Sensorion will provide a downgrade relationship as compared to the investigator's assessment.

Unrelated adverse events are those that are judged to be not related to the study or to the study drug by the investigator and the sponsor.

12.4 Premature study discontinuation due to adverse event

In the case of premature study treatment discontinuation due to an adverse event, the Investigator must immediately notify the monitoring team using the specific eCRF form.

12.5 Safety follow-up

- The Investigator should take all appropriate measures to ensure the safety of the subjects. All patient presenting with any AE should be followed up until normalization or the return to baseline conditions. Follow up may continue after the end of study visit
- In case of severe laboratory abnormalities, abnormal ECG, the test should be immediately repeated to confirm the value. If confirmed, the treatment should be discontinued and all appropriate measures should be taken to ensure the safety of the patient.

12.6 Unblinding procedure

In case of an emergency, the Investigator can unblind the treatment for a specific Patient.

Before breaking a Patient's blind, the Investigator must contact with the Medical Monitor or his/her Backup (available 24H/24, 7 days a week) to obtain a PIN code for unblinding in the IWRS.

In the event the system is unavailable, the investigator can call the IWRS helpdesk (the telephone numbers for the Helpdesk are listed in the IWRS Site User Guide) and provide the PIN. Helpdesk will break the blind and provide treatment nature to the investigator over the phone and a confirmation by email.

Unblinded subjects must be discontinued from the study

MEDICAL MONITOR CONTACT INFORMATION
[redacted]
BACKUP MEDICAL MONITOR
[redacted]

12.7 General Safety Monitoring

12.7.1 Safety steering committee

Sensorion Safety Steering Committee, independent from the monitoring study team, will meet periodically as determined appropriate for the individual protocol to review blinded safety data. These data will include but not be limited to:

- AEs of a Grade ≥ 3
- Non-serious AEs that result in an early study withdrawal
- Serious AEs
- Selected laboratory tests, as deemed appropriate by the Safety Steering Committee

The steering committee may ask for un-blinding of the data if needed. Appropriate action, if needed, will be taken based upon this review and in consultation with the study clinical team, as appropriate. The steering committee minutes and charter that will be established before the first patient will be included in the study documentation file for consultation by health authorities if needed. The steering committee may contact directly the DMC if there is any concern with regard to safety.

12.7.2 Data Monitoring Committee

An external data monitoring committee (DMC), independent from the sponsor and the monitoring team will be set up to review the safety of the product throughout the conduct of the study.

The committee consisting of two or more physicians and a statistician will be provided with the blinded safety information on a regular basis. Safety data will be provided by patient with relevant information according to the DMC charter that will be established before the first patient is included. The DMC may ask a total or partial un-blinding of the data. The first review is expected to be done after 30 patients have completed the study. The DMC will be responsible for providing recommendation for the continuation of the study, amendment or discontinuation. The DMC minutes and final recommendation will be included in the study documentation file.

13 STATISTICAL CONSIDERATIONS

The statistical considerations summarized in this section outline the plan for data analysis of this study. A statistical analysis plan (SAP) will be finalized prior to the database lock.

For continuous variables, descriptive statistics will include at least the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum.

For categorical data, frequencies and percentages will be displayed for each category.

SAS Version 9.2 or later will be used for statistical programming.

13.1 Determination of sample size

It was based on the area under the curve (AUC) of the Vertigo Intensity Visual Analogue Scale (VI-VAS) from baseline included to second measurement of Day 4 included. A sample size of 207 patients (69 patients per treatment group) was retained corresponding to the following assumptions:

- Each comparison to placebo performed at 2.5% two-sided significance level
- Power of each comparison to placebo set to 85%.
- 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).

13.2 Subject description

13.2.1 Disposition of subjects

The total number of subjects for each one of the following categories will be presented in the clinical study report (CSR) using a flow-chart diagram:

- Screened subjects,
- Included subjects (= randomized: those who receive a treatment number),
- Exposed subjects (those who take at least one dose of randomized study drug),
- Completed subjects,
- Reasons for treatment discontinuation.

In summary tables, a breakdown by center and randomized treatment group (3 groups as defined in section 7.1) will be given.

The total number of subjects screened and the reasons for screen failure will be presented separately.

The overall number of subjects who completed the study normally will be described by center. In addition, the number and percentage of subjects in each randomized treatment group who completed the study will be displayed in a table.

Reasons for study withdrawal will be supplied in tables giving numbers and percentage, broken down by randomized treatment group and in individual data listings, sorted by center and by subject.

For all categories of subjects but screened and included, percentages will be calculated using the number of randomized subjects as denominator.

13.2.2 Protocol deviations

Protocol deviations will be identified and classified. Only subjects with major deviations will be discussed in the clinical study report [CSR]. The deviations will also be considered in defining the PP population (major deviations only).

13.3 Analysis populations

13.3.1 Efficacy populations

13.3.1.1 Intent-to-Treat

The intent-to-treat (ITT) analysis set will comprise all randomized patients according to randomization group. All efficacy analyses will be performed on the ITT analysis set.

13.3.1.2 Per-protocol

The per-protocol (PP) analysis set will comprise all patients of the ITT analysis set without major protocol deviation. Selected efficacy analyses (primary efficacy endpoint, secondary endpoints) will be repeated on the PP analysis set.

13.3.2 Safety population

The safety analysis set will comprise all treated patients according to first treatment actually received.

13.4 Statistical methods

13.4.1 Analysis of primary efficacy endpoint

The VI-VAS AUC will be compared between treatment groups within an analysis of covariance model with the stratification factor (duration of vertigo before being treated) and the baseline score as covariates. Missing intermediate measurements won't be replaced in the calculation of the AUC, 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 or other.

The two comparisons to placebo will be tested with an alpha adjusted to the Dunnett's multiple comparison procedure in order to preserve an overall type I error of 5%, the corresponding confidence intervals will be presented.

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. 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 score 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. 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 two comparisons to placebo will be tested at each time using an alpha adjusted according to the Dunnett's multiple comparison procedure in order to preserve an overall type I error of 5% within the time considered and the corresponding confidence intervals will be presented.

13.4.2 Analysis of secondary efficacy endpoints

13.4.2.1 Worst spontaneous vertigo intensity over the 4 treatment days

The baseline and the 8 post-baseline assessments of the Worst VI-VAS will be analyzed using the approach described in section 13.4.1 for the primary endpoint.

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

The change from baseline of the total score of the Romberg tests (see section 10.1.7) at the end of treatment (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 before being treated) and the baseline total score. The two comparisons to placebo will be tested with an alpha adjusted according to the Dunnett's

multiple comparison procedure in order to preserve an overall type I error of 5%, the corresponding confidence intervals will be presented.

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

13.4.2.3 Peak slow phase velocity at the end of treatment and end of study

The change from baseline of the peak slow phase velocity (degrees/second, see section 10.1.7) at the end of treatment (D5) and the change from baseline at the end of study (D28) will be analyzed using the approach described in section 13.4.2.2 for the total score of the Romberg tests.

13.4.2.4 Nausea severity over the 4 treatment days

The baseline and the 8 post-baseline assessments of the Nausea Intensity VAS (see section 10.1.2) will be analyzed using the approach described in section 13.4.1 for the primary endpoint.

13.4.2.5 Functional disability at the end of study

The change from baseline of the DHI functional sub-score scale (see section 10.1.4) at the end of study (D28) will be compared between treatment groups within an analysis of covariance model. Patients without data available at the end of study will be excluded from the analysis. The two comparisons to placebo will be tested with an alpha adjusted to the Dunnett's multiple comparison procedure in order to preserve an overall type I error of 5%, the corresponding confidence intervals will be presented.

The same approach will be applied to the change from baseline of the VADL score (see section 10.1.5) at the end of study (D28).

13.4.3 Analysis of safety endpoints

The summary of safety will be presented by treatment group on the basis of the safety population. The analysis will be essentially descriptive and no hypothesis testing is planned.

13.4.3.1 Adverse events

Each adverse event will be coded to a “Preferred Term” and associated “System-Organ Class” according to an established and validated adverse reaction dictionary (MedDRA) before the randomized treatment code is broken. The adverse event endpoints are number of subjects experiencing:

- at least one event,
- an event under each recorded Preferred Term,
- an event under each recorded System-Organ Class.

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

All safety analyses will be performed on the safety analysis set using descriptive statistics.

Adverse events (AEs) will be evaluated for severity and coded using MedDRA. They will be summarized by system organ class and preferred term. Separate summaries of treatment-emergent AEs (TEAEs) will be generated for the following:

- All TEAEs
- Severe TEAEs
- Serious TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs resulting in death

Treatment-emergent adverse events (TEAE) are defined as events occurring after the first dose intake of randomized study drug, and up to and including five half-lives 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.

An AE that will not qualify as a TEAE will be considered as a Non-TEAE.

To understand the impact of subjects who withdraw from the study prior to completion, the FAS will be partitioned into groups of subjects who complete the study (completers) and subjects who do not complete the study (dropouts).

13.4.3.2 Clinical laboratory evaluations

Summary statistics for baseline, each post-baseline measurement, and change from baseline for each post-baseline measurement will be presented by treatment group for each haematology, blood chemistry and liver function testparameter.

The potentially clinically significant abnormality values will be defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review Number and percentage of patients presenting at least one post-baseline potentially clinically significant abnormality will be presented by treatment group for selected parameters.

Listings will be provided with flags indicating the out of laboratory range values and the potentially clinically significant abnormality values

13.4.3.3 Vital signs

The same approach as for the analysis of clinical laboratory evaluations will be used.

13.4.3.4 ECG

The same approach as for the analysis of clinical laboratory evaluations will be used.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Good clinical practice (GCP)

This clinical trial is conducted in accordance with the principles of the Declaration of Helsinki (1964), the International Conference on Harmonization Good Clinical Practice guideline. This clinical trial is also conducted in accordance with the laws and regulations of the countries in which the study is performed, as well as any applicable guidelines.

14.2 Informed consent

According to applicable regulatory requirements, the investigator or a fully designated person should provide the patient with a complete and detailed information about the aim, the consequences, the constraints of the trial, the favorable opinion given by the IRB, and any information deemed necessary both verbally and by reviewing the information leaflet and consent form. The subject must agree to perform the study, sign and date the Informed Consent form prior to any study-specific procedure. He will be given a copy of the information leaflet and consent form.

14.3 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The Investigator must submit the protocol and all the necessary documents (informed consent document and any materials provided to the patient) to the appropriate Ethics Committee (IRB/IEC), for review and approval, prior to any patient enrollment. Approval by IRBs is required for each participating site.

The investigator should notify the sponsor of the IRB's approval date. He should forward to the Sponsor a copy of the written and dated approval / favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition, prior to any investigational product drug shipment to the site.

Any amendment to the protocol should be submitted for approval to the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

15 STUDY MONITORING

15.1 Responsibilities of the Investigator

The Investigator undertakes to perform the study in accordance with this protocol, Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with the Investigational Product schedule, visit schedule and procedures required by the protocol. No protocol waivers will be accepted.

The Investigator agrees to complete all information requested in the electronic Case Report Form according to the instructions provided and to ensure direct access to source documents to Sponsor representatives.

The investigator is also responsible for recording all observations and other data pertinent to the clinical investigation.

The computerized handling of the data by the CRO after the data have been entered on the e CRFs may generate additional requests. The Investigator agrees to answer to these requests in a timely manner or to correct directly the e CRF when relevant.

15.2 Responsibilities of the Sponsor

The Sponsor of this study is responsible to Health Authorities for taking all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol compliance, integrity and validity of the data recorded on the Case Report Forms. Thus, the main duty of the Monitoring Team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the center will be contacted, through site visits, letters or telephone calls, by a representative of the Monitoring Team to review study progress, Investigator and subject compliance to protocol requirements and any emergent problems. During monitoring visits, the following points will be scrutinized with the Investigator: subject informed consent, subject recruitment and follow-up, study drug allocation, subject compliance with the Investigational Product, Investigational Product accountability, concomitant therapy use, Adverse Event documentation and reporting, and quality of data. Sections of Case Report Forms may be collected on a visit-by-visit basis.

Any protocol deviation will be assessed by the sponsor. In the event of breach of fundamental obligations including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the ICH guidelines on good clinical practice, the sponsor will report major non-compliance to health authorities.

15.3 Source document requirements

According to the guidelines on Good Clinical Practice, the Monitoring Team must check the Case Report Form entries against the source documents, except for the pre-identified source data directly

recorded in the Case Report Form. The Informed Consent Form will include a statement by which the subject allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to source data which supports the data on the Case Report Forms (e.g. subject's medical file, appointment books, original laboratory records, etc.). This personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

15.4 Protocol amendments

All appendices attached hereto and referred to herein are made part of this protocol.

No change or amendment to this protocol may be made by the Investigator or by the Sponsor after the protocol has been agreed to and signed by both parties unless such change(s) or amendment(s) has/have been fully discussed and agreed upon by the Investigator and the Sponsor. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this protocol.

No change or amendment to the protocol will be implemented prior to approval is received to the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

Any change or amendment to the protocol should be submitted for approval to the Ethics Committee (IRB/IEC) and regulatory authorities, and implemented only after approval is received, unless there are overriding safety reasons.

16 ADMINISTRATIVE RULES

16.1 Curriculum Vitae

An updated copy of the curriculum vitae limited to the experience, qualification and training for each Investigator and Sub-Investigator (and completed FDA 1572 form and Financial Disclosure Form study under an IND) will be provided to the Sponsor prior to the beginning of the study.

16.2 Record retention in study sites

The Investigator must maintain all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator must keep the study documentation for at least15 years, or longer if required by local regulatory requirements. The investigator should take all necessary measures to prevent accidental destruction of this documentation. The sponsor should be informed by the site prior to final destruction.

16.3 Confidentiality

The current protocol and any unpublished document referring to SENS-111 or to the current clinical trial provided by the sponsor (or any institution acting on their behalf) to the investigator or investigational staff member remains the exclusive property of Sensorion. They should not be disclosed to any person without prior written authorization from Sensorion.

The same confidentiality rules apply to all results, discoveries, data obtained from this clinical trial.

Only, submission of this protocol and necessary documents to the Ethics Committee (IRB/IEC) is authorized. Any documentation, record or result that may be requested by the sponsor or representatives of health authorities in the context of inspection is also authorized.

The investigator must ensure that the subject's anonymity is maintained, and keep in strict confidence documents not de-identified (e.g., signed informed consent form).

In case of an inspection by the authorities, the investigator shall inform the sponsor as soon as possible and authorized the sponsor to participate at this audit.

16.4 Ownership of data and use of the study results

All data, results, findings resulting from this clinical trial are the exclusive property of Sensorion. They can be used by Sensorion in any form for submission to health authorities of any country. In no case, the investigator or his/her staff member is authorized to file patent application referring to the results or discoveries generated by this clinical trial.

The investigator or any staff member participating in the study is authorized to present or to publish the study results after they have received a formal written and signed authorization from Sensorion. This authorization will be delivered after the review made by Sensorion. The authors should forward a copy

of the abstract or the text and slides of the presentation at least 7 days in advance prior to the submission. Sensorion may request to add the sponsor's name or the name of some employees on the manuscript.

16.5 Insurance compensation

The Sponsor certifies that it has taken out a liability insurance policy which covers the liability of the Investigator and his/her coworkers and which is in accordance with local laws and requirements. Specific statements will be contained in an appendix where needed.

An insurance certificate will be provided to the Investigator in countries requiring this document.

16.6 Premature discontinuation of the study or premature close out of a center

16.6.1 Decided by the Sponsor in the following cases

- The study is not conducted in accordance with the procedures defined in the approved protocol (i.e., low rate of recruitment - protocol deviations - failure to ensure the quality of the data collected).
- Information on the Investigational Product causing doubt as to the benefit/risk ratio.
- The total number of subjects included earlier than expected.
- Left at the discretion of the Sponsor.

16.6.2 Decided by the Investigator

The Investigator must notify the Sponsor of his/her decision and give the reason in writing.

In all cases Ethics Committees (IRB/IEC) and Health Authorities should be informed.

In some instances, an amendment may require a change to the Informed Consent Form. The Investigator must receive an IRB/IEC approval / favorable opinion concerning the revised Informed Consent Form prior to implementation of the change.

17 BIBLIOGRAPHIE

1. Thurmond RL. The histamine H4 receptor: from orphan to the clinic. *Front. Pharmacol*., 2015, 6:65
2. Dutia MB. Mechanisms of vestibular compensation: recent advances. *Current Opinion in Otolaryngology & Head and Neck Surgery*, 2010, 18:420-424.
3. Adamec I, Krbot SM, Handzic J, *et al*. Incidence, seasonality and comorbidity in vestibular neuritis. *Neurol Sci*. 2015, 36:91–5.
4. Agrawal Y, Carey JP, Hoffman HJ, Sklare DA, Schubert MC. The modified Romberg Balance Test: normative data in U.S. adults. Otology & neurotology: official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotogy 2011, 32(8):1309-11.
5. Bisdorff, A., B.M. Von, T. Lempert & D.E. Newman-Toker. Classification of vestibular symptoms: towards an international classification of vestibular disorders. *J. Vestib. Res*. 2009, 19: 1–13.
6. Chen L, Todd M, Halmagyi GM, *et al*. Head impulse gain and saccade analysis in pontine-cerebellar stroke and vestibular neuritis. *Neurology* 2014, 83:1513–22.
7. Newman-Toker DE, Kattah JC, Alvernia JE, *et al*. Normal head impulse test differentiates acute cerebellar strokes from vestibular neuritis. *Neurology* 2008, 70:2378–85.
8. Desmadryl G, Gaboyard-Niay S., Brugeaud A., TravoC., Broussy A., Saleur A., Dyhrfjeld-Johnsen J., Wersinger E., Chabbert C. *Br J Pharmac*ol. 2012, 167(4):905-16..
9. Feliszek, M, Speckmann, V, Schacht, D, *et al*. Naunyn Schmiedebergs A search for functional histamine H4 receptors in the human, guinea pig and mouse. *Naunyn-Schmiedeberg's archives of pharmacology* 2015, 388(1):11-7.
10. Godemann F, Linden M, Neu P, *et al*. A prospective study on the course of anxiety after vestibular neuronitis. *J Psychosom Res*. 2004, 56:351–354.
11. Godemann F, Siefert K, Hantschke-Bruggemann M, *et al*. What accounts for vertigo one year after neuritis vestibularis – anxiety or a dysfunctional vestibular organ? *J Pychiatr Res*. 2005, 39:529–534.
12. Greco A, Macri GF, Gallo A, Fusconi M, De Virgilio A, Pagliuca G, Marinelli C, de Vincentis M. Is vestibular neuritis an immune related vestibular neuropathy inducing vertigo. *J.Immunol Research*. 2014, 14:1-8.
13. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. *Arch Otolaryngol Head Neck Surg.* 1990, 116(4):424–7
14. Kinaka Y, Sektani T, Okazaki H, *et al*. Progress of caloric response of vestibular neuronitis. *Acta Otolaryngol Suppl*. 1993, 503:18–22.
15. Mégnigbêto AC, Sauvage JP, Launois R. The European Evaluation of Vertigo scale (EEV): A clinical validation study. *Revue Laryngologie Otologie Rhinologie*. 2001, 122 (2): 95 -102.
16. Milionis HJ, Mittari V, Exarchakos G, Kalaitzidis R, Skevas AT, Elisaf MS. Lipoprotein and acute-phase response in patients with vestibular neuronitis. *Eur J Clin Invest.* 2003, 33 (12):1045-50.

17. Neuhauser HK. Epidemiology of vertigo. *Curr Opin Neurol* 2007, 20:40–6.
18. Neuhauser HK, von Brevern M, Radtke A, Lezius F, Feldmann M, Ziese T, *et al*. Epidemiology of vestibular vertigo: a neurotologic survey of the general population. *Neurology*. 2005, 65(6): 898–904.
19. Reilly MC, Zbrozek AS, Dukes E. The validity and reproducibility of a work productivity and activity impairment measure. *PharmacoEconomics* 1993, 4(5):353-365.
20. Schneider EH, Neumann D, Seifert R. Histamine H4 receptor in the brain? *Naunyn Schmiedebergs Arch Pharmacol.* 2015, 388(1):5-9
21. Sekitani T, Imate Y, Noguchi T, *et al*. Vestibular neuronitis: epidemiological survey by questionnaire in Japan. *Acta Otolaryngol (Stockh) Suppl*. 1993, 503:9–12.
22. Strupp M, Brandt T. Vestibular neuritis. *Semin Neurol.* 2009, 29:509–19.
23. Strupp M, Zingler VC, Arbusow V, *et al*. Methylprednisolone, valacyclovir, or the combination for vestibular neuritis. *N Engl J Med* 2004, 35:354–61.
24. Strupp M, Magnusson M. Acute unilateral vestibulopathy. *Neurol Clin*. 2015, 33(3) 669–685.
25. Takeda N, Morita M, Hasegawa S, Horii A, Kubo T, Matsunaga T. Neuropharmacology of motion sickness and emesis. A review. *Acta Otolaryngol Suppl*. 1993, 501:10-5. Review.
26. Takeda N, Morita M, Horii A, Nishiike S, Kitahara T, Uno A. Neural mechanisms of motion sickness. *J Med Invest*. 2001, 48 (1-2):44-59. Review.
27. Takumida M, Takumida H, Anniko M: Localization of histamine (H_1, H_2, H_3 and H_4) receptors in mouse inner ear. *Acta Otolaryngol*. 2016, 136 (6):537-44.
28. Yardley L, Burgneay J, Andersson G, Owen N, Nazareth I, Luxon L: Feasibility and effectiveness of providing vestibular rehabilitation for dizzy patients in the community. *Clin Otolaryngol* 1998, 23:442-448.
29. Yardley L, Masson E, Verschuur C, Haacke N, Luxon L. Symptoms, anxiety and handicap in dizzy patients: development of the vertigo symptom scale. *J Psychosom Res.* 1992, 36(8):731–41.
30. Cowden JM, Yu F, Banie H, Farahani M, Ling P, Nguyen S, Riley JP, Zhang M, Zhu J, Dunford PJ, Thurmond RL. The histamine H4 receptor mediates inflammation and Th17 responses in preclinical models of arthritis. *Ann Rheum Dis.* 2014, 73(3):600-8.
31. Son EJ Lee DH, Oh JH, Seo JH, Jeon EJ. Correlation between the dizziness handicap inventory and balance performance during the acute unilateral vestibulopathy. *Am J Otolaryngol.* 2015, 36(6):823-7
32. Kammerlind A-S, Larsson PB, Ledin T, Skargren E. Reliability of clinical balance tests and subjective ratings in dizziness and disequilibrium. *Advances in Physiotherapy.* 2005, 7(3):96–107
33. Kammerlind AS, Ledin TE, Odkvist LM, Skargren EI. Recovery after acute unilateral vestibular loss and predictors for remaining symptoms. *Am J Otolaryngol.* 2011, 32(5):366-75.
34. Dannenbaum E, Chilingaryan G, Fung J. Visual vertigo analogue scale: an assessment questionnaire for visual vertigo. *J Vestib Res.* 2011, 21(3):153–9.
35. Housley GD, Norris CH, Guth PS. *Hear Res.* 1988, 35(1):87-97

36. Beck R, Gunther L, Xiong G *et al*. The mixed blessing of treating symptoms in acute vestibular failure - Evidence from a 4-aminopyridine experiment. *Exp Neurol.* 2014, 261:638-45.
37. Strupp, M. MD; Arbusow, V. MD; Maag, K. P. MD, PhD; Gall, C. MD; Brandt, T. Vestibular exercises improve central vestibulospinal compensation after vestibular neuritis. *Neurology*. 1998, 51(3):838-844.
38. Shupak A, Issa A, Golz A, Margalit Kaminer, Braverman I. Prednisone treatment for vestibular neuritis. *Otol Neurotol.* 2008, 29(3):368-74.
39. Cohen H.S., Kimball K.T., Development of the Vestibular Disorders Activities of Daily Living Scale. *Arch Otolaryngol Head Neck Surg*. 2000, 126:881–887.
40. Helmchen C., Klinkenstein J.C., Krüger A., Gliemroth J., Mohr C. and Sander T., Structural brain changes following peripheral vestibulo-cochlear lesion may indicate multisensory compensation. *J Neurol Neurosurg Psychiatr.* 2011, 82:309– 316.

18 APPENDICES

Appendix 1. **Standing Vertigo Intensity Visual Analog Scale**

Patients should rate the intensity of the vertigo just after the Romberg test condition 1 (eyes open, feet together, standing on a firm surface) performed in the morning between 10am and 12pm, and in the evening while at the study site just after dinner using the electronic device*. An alert will remind the patient to complete the VAS.
The study staff will be responsible to instruct the patient how to complete the VAS before the first inquiry using the test page. The patient should move the virtual cursor to place the mark on the VAS horizontal line, on the electronic device.
If the patient is unable to complete the VAS while hospitalized, the nurse or the investigator should ask the patient how much he would rate the severity of his/her vertigo on a 0 to 100 scale. The figure should be reported on the eCRF and the reason of missing data completed as follows: not able to stand up, severe vertigo, severe nausea or other
When the patient is at home, the patient will be instructed to continue to rate the intensity of the vertigo when he/she is standing up, feet together, eyes open, in the morning between 10am and 12pm, and in the evening just after dinner using the electronic device. An alert will remind the patient to complete the VAS. If the patient is unable to complete the VAS, he/she will have to provide the reason in the electronic device no later than 24 hours later.

Place a mark on the line to indicate the severity of your vertigo (when you stand up, feet together, eyes open)

No vertigo Worst vertigo ever

The line should measure exactly 100 mm

Example:

* Patients will be provided with an electronic device Samsung Galaxy TAB E: 9.6" (243.4mm) screen size and 1280 x 800 (WXGA)resolution with a blocked zooming function. This is to ensure the VAS line measures exactly 100mm, along the study.

Appendix 2. **Worst Vertigo Intensity Visual Analog Scale**

Patients should rate the intensity of the most severe vertigo over the last 2 hours in the morning between 10am and 12pm, and in the evening just after dinner using the electronic device*. An alert will remind the patient to complete the VAS twice daily.
The study staff will be responsible to instruct the patient how to complete the VAS before the first inquiry using the test page. The patient should move the virtual cursor to place the mark on the VAS horizontal line, on the electronic device.
If the patient is unable to complete the VAS while hospitalized, the nurse or the investigator should ask the patient how much he would rate the severity of his/her vertigo on a 0 to 100 scale. The figure should be reported on the e CRF and the reason of missing data completed as follows: severe vertigo, severe nausea or other
If the patient is unable to complete the VAS at home, he/she will have to provide the reason in the electronic device no later than 24 hours later.

Place a mark on the line to indicate the intensity of your worst vertigo over the past 2 hours

No vertigo Worst vertigo ever

The lines should measure exactly 100 mm

* Patients will be provided with an electronic device Samsung Galaxy TAB E: 9.6" (243.4mm) screen size and 1280 x 800 (WXGA)resolution with a blocked zooming function. This is to ensure the VAS line measures exactly 100mm, along the study.

Appendix 3. **Nausea Intensity Visual Analog Scale**

Patients should rate the intensity of the nausea in the morning between 10am and 12pm, and in the evening just after dinner using the electronic device*, considering the worst intensity over the past 2 hours. An alert will remind the patient to complete the VAS. The patient should place a vertical line on the VAS horizontal line that will be shown on an electronic tablet.
The study staff will be responsible to show how to complete the VAS before the first inquiry using the test page.

Place a mark on the line to indicate the severity of your nausea (the worst over the last 2 hours)

No nausea Worst nausea ever

The line should measure exactly 100 mm

Example:

* Patients will be provided with an electronic device Samsung Galaxy TAB E: 9.6" (243.4mm) screen size and 1280 x 800 (WXGA)resolution with a blocked zooming function. This is to ensure the VAS line measures exactly 100mm along the study.

Appendix 4. **DHI – Dizziness Handicap Inventory**

Instructions: The purpose of this scale is to identify difficulties that you may be experiencing because of your dizziness. Please check "yes", or "no" or "sometimes" to each question. Answer each question only as it pertains to your dizziness problem.

	Questions	Yes	Sometimes	No
P1	Does looking up increase your problem?			
E2	Because of your problem, do you feel frustrated?			
F3	Because of your problem, do you restrict your travel for business or recreation?			
P4	Does walking down the aisle of a supermarket increase your problem?			
F5	Because of your problem, do you have difficulty getting into or out of bed?			
F6	Does your problem significantly restrict your participation in social activities, such as going out to dinner, going to movies, dancing or going to parties?			
F7	Because of your problem, do you have difficulty reading?			
P8	Does performing more ambitious activities such as sports, dancing, and household chores, such as sweeping or putting dishes away increase your problem?			
E9	Because of your problem, are you afraid to leave your home without having someone accompany you?			
E10	Because of your problem, have you been embarrassed in front of others?			
P11	Do quick movements of your head increase your problem?			
F12	Because of your problem, do you avoid heights?			
P13	Does turning over in bed increase your problem?			
F14	Because of your problem, is it difficult for you to do strenuous housework or yard work?			
E15	Because of your problem, are you afraid people may think you are intoxicated?			

F16	Because of your problem, is it difficult for you to go for a walk by yourself?			
P17	Does walking down a sidewalk increase your problem?			
E18	Because of your problem, is it difficult for you to concentrate?			
F19	Because of your problem, is it difficult for you to walk around your house in the dark?			
E20	Because of your problem, are you afraid to stay home alone?			
E21	Because of your problem, do you feel handicapped?			
E22	Has your problem placed stress on your relationship with members of your family or friends?			
E23	Because of your problem, are you depressed?			
F24	Does your problem interfere with your job or household responsibilities?			
P25	Does bending over increase your problem?			

Scoring for the Dizziness Handicap Inventory:

The sum of each rating calculated with Always = 4 Sometimes = 2 No = 0 is the perceived disability scoring. The highest score is 100 (maximum perceived disability), and the minimum score is 0 (no perceived disability).

3 subscales are established to track the specific changes:

P = physical

E = emotional

F = function

Appendix 5. **Vestibular Disorders Activities of Daily Living Scale**

Vestibular Disorders Activities of Daily Living Scale

Name/ID_____ Rater_____ Date_____

Instructions

This scale evaluates the effects of vertigo and balance disorders on independence in routine activities of daily living. Please rate your performance on each item. If your performance varies due to intermittent dizziness or balance problems please use the greatest level of disability. For each task indicate the level which most accurately describes how you perform the task. If you never do a particular task, please check the box in column NA. The rating scales are explained on bottom of page.

	Independence Rating										
	Independent	*Uncomfortable, No Change in Ability*	*Decreased Ability, No Change in Manner of Performance*	*Slower, Cautious, More Careful*	*Prefer Using an Object for Help*	*Must Use an Object for Help*	*Must Use Special Equipment*	*Need Physical Assistance*	*Dependent*	*Too Difficult, No Longer Perform*	
Task	1	2	3	4	5	6	7	8	9	10	NA
F-1 Sitting up from lying down											
F-2 Standing up from sitting on the bed or chair											
F-3 Dressing the upper body (eg, shirt, brassiere, undershirt)											
F-4 Dressing the lower body (eg, pants, skirt, underpants)											
F-5 Putting on socks or stockings											
F-6 Putting on shoes											
F-7 Moving in or out of the bathtub or shower											
F-8 Bathing yourself in the bathtub or shower											
F-9 Reaching overhead (eg, to a cupboard or shelf)											
F-10 Reaching down (eg, to the floor or a shelf)											
F-11 Meal preparation											
F-12 Intimate activity (eg, foreplay, sexual activity)											
A-13 Walking on level surfaces											
A-14 Walking on uneven surfaces											
A-15 Going up steps											
A-16 Going down steps											
A-17 Walking in narrow spaces (eg, corridor, grocery store aisle)											
A-18 Walking in open spaces											
A-19 Walking in crowds											
A-20 Using an elevator											
A-21 Using an escalator											
I-22 Driving a car											
I-23 Carrying things while walking (eg, package, garbage bag)											
I-24 Light household chores (eg, dusting, putting items away)											
I-25 Heavy household chores (eg, vacuuming, moving furniture)											
I-26 Active recreation (eg, sports, gardening)											
I-27 Occupational role (eg, job, child care, homemaking, student)											
I-28 Traveling around the community (car, bus)											

Explanation of Independence Rating Scale

This scale will help us to determine how inner ear problems affect your ability to perform each task. Please indicate your current performance on each task, as compared to your performance before developing an inner ear problem, by checking one of the columns in the center of the page. Pick the answer that most accurately describes how you perform the task.

1. I am **not disabled,** perceive no change in performance from before developing an inner ear impairment.
2. I am **uncomfortable** performing the activity but **perceive no difference** in the quality of my performance.
3. I **perceive a decrement** in the quality of my performance, **but have not changed** the manner of my performance.
4. I **have changed** the manner of my performance, eg, I do things more slowly or carefully than before, or I do things without bending.
5. I **prefer using an ordinary object** in the environment for assistance (eg, stair railing) but I am not dependent on the object or device to do the activity.
6. I **must use** an ordinary object in the environment for assistance, but I have not acquired a device specifically designed for the particular activity.
7. I must use **adaptive equipment** designed for the particular activity (eg, grab bars, cane, reachers, bus with lift, wedge pillow).
8. I require another person for **physical assistance** or, for an activity involving 2 people, I need unusual physical assistance.
9. I am **dependent** on another person to perform the activity.
10. I **no longer perform** the activity due to vertigo or a balance problem.

NA. I **do not usually perform this task** or **I prefer not to answer** this question.

Appendix 6. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)

The following questions ask about the effect of your VERTIGO on your ability to work and perform regular activities. *Please fill in the blanks or select a number, as indicated.*

1. Are you currently employed (working for pay)? _____NO ___ YES

If NO, check "NO" and skip to question 6.

The next questions are about the past seven days, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your VERTIGO? Include hours you missed on sick days, times you went in late, left early, etc., because of your VERTIGO. Do not include time you missed to participate in this study.
_____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
_____HOURS

4. During the past seven days, how many hours did you actually work?
_____HOURS
(If "0", skip to question 6.)

5. During the past seven days, how much did your VERTIGO affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If VERTIGO affected your work only a little, choose a low number. Choose a high number if VERTIGO affected your work a great deal.

Consider only how much VERTIGO affected productivity while you were working.

VERTIGO had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	VERTIGO completely prevented me from working

SELECT A NUMBER

6. During the past seven days, how much did your VERTIGO affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If VERTIGO *affected your activities only a little, choose a low number. Choose a high number if* VERTIGO *affected your activities a great deal.*

Consider only how much VERTIGO affected your ability to do your regular daily activities, other than work at a job.

VERTIGO had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	VERTIGO completely prevented me from doing my daily activities

SELECT A NUMBER

Questions:
1 = currently employed
2a = hours missed due to specified problem
2b = hours missed due to other health problems
2c = hours missed other reasons
3 = hours actually worked
4a = degree problem affected productivity while working
4b = degree other health problems affected productivity while working
5a = degree problem affected regular activities
5b = degree other health problems affected regular activities

Scores:
Percent work time missed due to problem: Q2a/(Q2a+Q2b+Q3)

Percent impairment while working due to problem: Q4a/10

Percent overall work impairment due to problem: Q2a/(Q2a+Q2b+Q3) + {(1-(Q2a+Q2b)/(Q2a+Q2b+Q3)) x Q4a/10

Percent activity impairment due to problem: Q5a/10

Percent work time missed due to all health: (Q2a+Q2b)/(Q2a+Q2b+Q3)

Percent impairment while working due to all health: (Q4a+Q4b)/10

Percent overall work impairment due to all health: (Q2a+Q2b)/(Q2a+Q2b+Q3) + {(1-(Q2a+Q2b)/(Q2a+Q2b+Q3)) x (Q4a+Q4b)/10

Percent activity impairment due to all health: (Q5a+Q5b)/10
WPAI:SHP V2.0 (US English)

Appendix 7. **Unassisted walking**

Patient will have to express their ability to walk without assistance on the electronic device twice daily in the morning and in the evening at the time of the VAS completion.

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"Because of your vertigo (or disequilibrium) problem, do you have difficulty walking 10 meters (32,8 feet) at your usual speed without using support? "

YES NO

.

Appendix 8. **Videooculography**

VOG testing is used to determine if a vestibular (inner ear) disease may be causing a balance or dizziness problem, and is one of the only tests available today that can distinguish between a unilateral (one ear) and bilateral (both ears) vestibular loss. In non-compensated unilateral vestibular dysfunction, the difference in the strength and nature of the nystagmus of the undermost vs. the uppermost ear during positional and positioning tasks can be observed and recorded.

A standardized portable VOG will be used by all centers to assess the spontaneous nystagmus intensity. Recordings will be considered as row data.

The portable VOG/EOG system is a goggle head mounted system with at least one digital camera connected to and powered by a computer (laptop) through a firewire connection.

Eye movements are recorded and converted to digital data. For analysis of horizontal and vertical components, the XY center of the pupil is first calculated. The use of digital centering eliminates the need for a mechanical adjustment mechanism (e.g. a slide) in the given direction. Using digital centering for both the X and Y (yaw and pitch) directions eliminates any gross adjustment in those directions.

The VOG system also incorporates a head fixed calibration mechanism in the form of an integrated laser pointer on the goggle base or camera housing. The calibration mechanism is incorporated directly into the goggle base and powered from the same source powering the digital cameras.

To monitor the movements of the eyes, infrared goggles are placed around the eyes to record eye movements during testing. Eye position will be calibrated using laser targets projected forward from the goggles

VOG testing is non-invasive, and only minor discomfort is felt by the patients during testing as a result of wearing goggles. Patients with dark eyelashes, drooped eyelids, may require their eye to be taped.

Appendix 9. Video head impulse test

The examiners will need to have training and experience, and their accuracy in performing h-HIT VOR measures will be monitored for consistency by assessing the rate of failed HIT maneuvers (i.e. those automatically rejected by the device software).

Patients will be asked to fix their gaze on a distant target (>1.5 m) while seated.

A series of inward HITs (i.e. centripetal, lateral-to- center head rotations) toward each ear will be performed by the examiner placing his/her hand on the patient's jaw or holding the patient's head on the top depending on the examiner's position either in front or behind the patient.

Target head velocity should be between 100 and 200°/s and head displacement between 5 and 20°. At least 10 finally non-rejected (captured and automatically processed) HITs will be required. If spontaneous nystagmus is present, VOR gain measures will be calculated accounting for the spontaneous slow-phase drift of the eye, with the device software operating in the nystagmus-adjusted interpretation mode.

Appendix 10. Romberg tests procedure

The procedure is designed to assess the patient's ability to stand unassisted under six successive test conditions of increasing difficulty.

Before starting the first test, the operator will identify the patient's dominant foot by asking which foot the patient would use to kick a ball. It will be recorded on the e CRF.

The operator will ask the patient to stand, shoes off, with his (or her) arms hanging down, and to not speak during the time interval. The patient should breathe normally and try to relax as much as possible, concentrating on the procedure. In case of talking, the trial is stopped and repeated.

The first 2 condition tests will be performed on the floor (hard surface). The 4 subsequent conditions will be performed on a foam pad standardized across sites.

Condition 1: Standing on the floor, feet together (or at a distance for them to be steady) with the eyes open looking straight ahead

Condition 2: Standing on the floor, feet together (or at a distance for them to be steady) with the eyes closed

Condition 3: Standing on a foam pad, feet together (or at a distance for them to be steady) with the eyes open looking straight ahead

Condition 4: Standing on a foam pad, feet together (or at a distance for them to be steady) with the eyes closed

Condition 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)

Condition 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).

Each of the condition will last for at least 5 seconds. They will be timed using a stop watch.

In order to prevent any fall, the operator will stand in front of the patient with his arms extended on either side of the patient but without touching him. If possible the patient will be close to a wall.

Each condition is scored 1 for a success and 0 for a failure.

The failure is defined as:

- The subject cannot stand up, and is unable to do the test or

- Any occurrence of any of the following within 5 seconds:
  - Movement of the subject's feet from the initial test position (falling, side-stepping, hopping, pivoting, etc.);
  - Eyes open during an eyes-closed condition (i.e., Conditions 2 and 4); or
  - Requirement of the operator intervention to prevent the subject from falling or to maintain balance.

Increased sway without movement of the feet do not constitute a failure:

In case of failure, the patient will have one more attempt to pass.

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 balance test will be repeated twice daily until the end of hospitalization, and then on Day 5 and Day 28 at the investigational site.

While the mentality that an examinee could fall at any time is critical to being ready to prevent a fall, note that the following times during the test pose the greatest risk of destabilization:

- While the examinee is stepping onto the foam and placing his or her feet together;
- While the examinee is stepping off the foam;
- During the first 3 seconds of a new test condition; and
- During Test Conditions 3 to 6 (with greater risk during Condition 4 and 6).

Appendix 11. Highly effective birth control methods

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation :
  - o oral
  - o injectable
  - o implantable
- intrauterine device (IUD)[1]
- intrauterine hormone-releasing system (IUS) [1]
- bilateral tubal occlusion[1]
- vasectomised partner [1 2]
- sexual abstinence [3]

Birth control methods that result in a failure rate of more than 1% per year are considered **not highly effective** and are therefore not accepted per protocol. They include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide[4]
- Cap, diaphragm or sponge with spermicide[4]

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

1. **Contraception methods that in the context of this guidance are considered to have low user dependency.**
2. **Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.**
3. **In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period study and 1 month after the end of the study drug intake. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.**

4. **A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective birth control methods**

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

19 LIST OF RAW DATA

Study data which should be included in the source dossier:

- Subject's identity.
- Pathology studied, date of diagnosis.
- Medical history, associated diseases (dates of onset).
- Dates and time of administration of the study drug.
- Previous and concomitant treatments.
- Dates of participation in the study.
- A statement that the informed consent form was signed by the subject.
- Dates of study visits.
- Examinations or assessments carried out during the study:
- Vital signs: temperature, systolic (SBP) and diastolic (DBP) blood pressures, heart rate, and respiration after 10 minutes rest in the supine and after 2 minutes in the standing position.
- Questionnaires scores
- Romberg tests results
- Oculography tracings
- Adverse events (+ follow-up).
- Date of drop-out and reason.
- Pregnancy test results
- Laboratory test results
- ECG