2. SYNOPSIS

Name of Sponsor: Sensorion SA	**(For National Authority Use only)**
Name of Finished Product: SENS-111	
Name of Active Ingredient: Selective histamine H_4 receptor antagonist	
TITLE OF STUDY:	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
PRINCIPAL INVESTIGATOR:	Prof. Dr. med Dr. h.c. Michael Strupp, FANA Neurologische Klinik Klinikum der Universität München Marchioninistr. 15, 81377 München Germany
STUDY CENTERS:	Multicenter
PUBLICATION (REFERENCES):	None
STUDY PERIOD:	Date of First Consent: 16-Aug-2017 Date of Last Follow-up Visit: 15-Oct-2019
PHASE OF DEVELOPMENT:	Phase 2
OBJECTIVES:	
Primary:	The primary objective was to assess the efficacy of SENS-111 in acute unilateral vestibulopathy (AUV).
Secondary:	The secondary objectives were: • 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 subjects 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 subjects with AUV • To evaluate the preliminary health economics of SENS-111
METHODOLOGY:	This was a double-blind, randomized, 3 parallel-group, and placebo-controlled international study. The study assessed the efficacy and safety of orally administered SENS-111 in subjects with AUV. Subjects were included if they presented with an acute unilateral peripheral vertigo lasting more than 6 hours and less than 3 days, diagnosed as an AUV, with an intensity of the vertigo of at least 60 mm on a 100 mm visual analog scale (VAS) measured in standing position with feet together. It was planned to enroll 105 subjects into the study: 35 subjects were to receive SENS-111 200 mg daily for 4 days, 35 subjects were to receive SENS-111 100 mg once daily for 4 days, and 35 subjects were to receive matching placebo (1:1:1 ratio). An additional dose (respectively 200 mg, 100 mg, and placebo) was administered in a blinded fashion to subjects approximately 12 hours after the first intake.

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The screening evaluation included vital signs, a complete oto-neurological examination, and nausea and vertigo evaluation to confirm the diagnosis. Subjects had to have met all inclusion and no exclusion criteria to be eligible. Specific attention was paid to exclude any subject with a history of stroke (a negative past magnetic resonance imaging was needed for inclusion of subjects with possible stroke of the brainstem or cerebellum). Following this screening phase, eligible subjects underwent a nystagmus evaluation with a video-oculography (VOG), and either a head impulse test, a caloric test, or both to confirm the diagnosis. Before the first intake of the investigational medicinal product (IMP) at the investigational site, the subjects completed vertigo evaluations with Vertigo Intensity Visual Analogue Scales (VI-VASs) and questionnaires, assessment of imbalance (Romberg tests), and nausea and vomiting scales. Subjects were requested to remain at the site for at least 6 hours after the first IMP intake to ensure subjects' safety. Approximately 12 hours after the first IMP intake, vital signs were assessed and a blood sample was taken for pharmacokinetic (PK) evaluation just before the second dose was given. In cases where a PK sample could not be taken at Hour (H) 12 or H24, it was acceptable to take a PK sample before the fourth dose (H48).

Subjects were asked to complete a VAS for vertigo intensity and nausea intensity twice daily using a specific electronic device in the morning between 10.00 am and 12.00 pm, and in the evening after dinner until the end of the study, and to record their ability to walk without support. The worst intensity of the spontaneous vertigo over the preceding 2 hours was recorded, as well as the intensity of vertigo while standing.

At 24 hours after the first IMP administration, subjects were tested with VOG to measure the severity of their spontaneous nystagmus; a PK blood sample was also taken immediately before the IMP administration. Subjects were regularly monitored for vertigo, nausea and vomiting, vital signs (both supine and standing), ability to walk unassisted, and imbalance (Romberg tests) until their discharge from the hospital, at which time a full efficacy assessment was performed, including assessment of the quality of life and VOG. The same assessments were performed at the following visit on Day (D) 5 and at the end of the study on D28. The additional assessments planned during the hospitalization period (i.e., Romberg test twice a day and video-nystagmography once a day) were optional.

Subjects were followed for adverse events (AEs) throughout the study until D28. Inquiry about potential AEs was made at every on-site visit and on D14, when a phone call was made to the subject.

Safety parameters included routine blood tests (complete blood count, chemistry, liver function tests, and lipid profile), urine analysis, pregnancy tests (if applicable), cardiac evaluation using electrocardiogram (ECG), physical examinations, and vital signs (with attention to orthostatic blood pressure).

A health economic questionnaire was completed at the end of the study.

At some specific sites, an ancillary (ANC) test using the vHIT or caloric test was conducted.

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NUMBER OF SUBJECTS (PLANNED AND ANALYZED):	Planned	105	Screened	134	Randomized	107
	Withdrawn	13	Completed	94		
	Analyzed (Safety)	104	Analyzed (Efficacy)	107	Analyzed (PK)	104
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:	Subjects were men or women ≥18 years and <75 years of age, suffering from an acute episode of vertigo of peripheral origin defined as severe (≥60mm on the standing VI-VAS), prolonged (more than 6 hours and less than 72 hours), associated with imbalance and/or postural imbalance, nausea and/or vomiting, with a spontaneous nystagmus toward the unaffected ear (fast phase), which was suppressed or reduced by visual fixation confirmed by oculography and a gain of the vestibulo-ocular reflex (VOR) <0.7, measured by the video-head impulse test (vHIT) and/or difference between the 2 labyrinths >25% according to the caloric test (de Jongkees' formula). Potential subjects with the following characteristics were excluded: acute hearing loss during or after the onset of the episode of vertigo; acute unilateral tinnitus; history of acute or chronic vestibular diseases; ongoing benign paroxysmal positional vertigo; history of acute central vestibular lesion; history of cochlear implants; stroke, brainstem, or cerebellar dysfunction; past or concomitant treatment with ototoxic chemotherapy; history of seizures or convulsions; head trauma within 10 days of randomization; history of malignancy other than cervical carcinoma-in-situ or non-metastatic basal cell or squamous cell skin carcinoma within 5 years. Subjects were excluded in case of pregnancy or if they were unwilling to use highly effective contraception while enrolled on study and for at least 1 month after the last IMP intake.					
TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, LOT NUMBERS:	Product name: SENS-111 Unit dose: 100 mg orally disintegrating tablet (ODT) Regimen: Twice a day on D1 (12 hours apart) and once a day on D2 to D4 Mode/route: Oral. The drug was to be kept in the mouth until complete dispersion. Dosing by treatment group: • SENS-111 100 mg: 2 ODT (1 ODT SENS-111 and 1 ODT placebo) • SENS-111 200 mg: 2 ODTs SENS-111 • Placebo: 2 placebo ODTs Lot numbers: • SENS-111 100 mg tablets – lot numbers 1611943 and 1663508 • Placebo tablets – lot numbers 1611942 and 1663507					
DURATION OF TREATMENT:	Study treatment was administered for 4 days.					
ENDPOINTS:						
Efficacy:	The primary endpoint was the vertigo intensity measured by the area under the curve (AUC) of the Vertigo Intensity Visual Analogue Scale (VI-VAS) in standing position over the 4 treatment days (8 post-baseline assessments). Secondary efficacy endpoints included comparisons between groups of the following: • Worst spontaneous vertigo intensity measured by the AUC of the worst VI-VAS over the 4 treatment days (8 post-baseline assessments)					

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	• Change from Baseline of the total score of the Romberg tests at the end of treatment (EOT) (D5) and end of study (EOS) (D28) • Change from Baseline in the peak slow phase velocity of the peripheral vestibular spontaneous nystagmus, measured by oculography in darkness at EOT (D5) and EOS (D28) • Nausea severity measured by the AUC of the Nausea Intensity Visual Analogue Scale (NI-VAS) over the 4 treatment days (8 post-baseline assessments) • Change from Baseline of the functional disability at the EOS (D28) assessed by the Dizziness Handicap Inventory (DHI) functional sub-scale score • The functional disability at EOS (D28) as assessed by the Vestibular Disorders Activities of Daily Living Scale (VADL)
Pharmacokinetics:	Serum samples were collected for PK analysis at 3 time points: hour (H) 12, H24, and at EOT Visit (D5). In cases where a PK sample could not be taken at H12 or H24, it was acceptable to take a PK sample before the fourth intake (H48). Plasma concentration of SENS-111 were used as parameters to describe the plasma exposure to SENS-111.
Safety:	The safety endpoints included AEs, laboratory results, vital sign measurements, and ECG findings.
Exploratory Efficacy:	Exploratory endpoints included the following comparisons: • Vertigo Intensity in standing position at the end of the study (D28) assessed by the VI-VAS • Worst spontaneous vertigo at the end of the study (D28) assessed by the VI-VAS • Time to unassisted walk • Health economic evaluation assessed with the Work Productivity and Activity Impairment and Specific Health (WPAI-SHP) questionnaire at the EOS
Ancillary:	Additional tests were performed at Baseline and at the end of the study in sites participating in the ANC study: • Video-head impulse test (vHIT), which provides a quick and objective measure of the vestibulo-ocular reflex (VOR) in response to head movements • Caloric test, which provides two parameters: total response (TR) and relative vestibular reduction (RVR)
STATISTICAL METHODS:	The sample size was based on the AUC of the VI-VAS from Baseline to the second measurement of D4. A sample size of 105 subjects (35 subjects per treatment group) was planned corresponding to the following assumptions: • Each comparison to placebo performed at 5% 1-sided significance level • Power of each comparison to placebo set to 75% • Randomization ratio 1:1:1 • Intra-group standard deviation (SD) of 71 mm/day • Difference to placebo of 40 mm/day (i.e., 20% of an average AUC of 200 mm/day on placebo)

The following populations were analyzed for this study:

- Screened population: The screened population included all screened and consented subjects. This population was used for subject disposition only.
- Safety population: The safety population included all treated subjects according to first treatment actually received.
- Intent-to-treat (ITT) population: The ITT population included all randomized subjects.
- Modified ITT (mITT) population: The mITT population included all subjects of the ITT population with a unilateral AUV (diagnosed before or after the randomization), a baseline standing VI-VAS ≥60 mm, and with at least 1 IMP intake.
- Per-protocol (PP) population: The PP population included all subjects of the mITT population with the primary efficacy endpoint (AUC for the standing VI-VAS) available and without a protocol deviation likely to impact the primary efficacy endpoint.
- Ancillary (ANC) population: The ANC included all subjects performing ancillary tests, i.e., video-head impulse test (vHIT) and/or caloric test.

The list of protocol deviations, likely to impact the primary efficacy endpoint, was finalized during a blind data review meeting on 12-Nov-2019 prior to the database lock.

The ITT population was the primary population for the efficacy analysis. The PP population was the secondary population for the efficacy analysis. The mITT population was used for a sensitivity efficacy analysis in a selection of endpoints: standing VI-VAS, worst VI-VAS, and NI-VAS. The safety population was used for the analyses of safety endpoints.

All efficacy analyses were conducted according to the randomized treatment assigned by interactive web response system; all safety analyses were conducted according to the treatment actually received.

The standing VI-VAS was summarized using descriptive statistics of absolute values and changes from Baseline at each assessment and of the AUC including the length of the AUC observation period. In this analysis, Baseline was defined as the first observation recorded in the electronic subject-reported outcome measure on the day of randomization or otherwise as the last observation before the day of randomization. The AUC calculation was conducted using all VAS assessments between Baseline and Baseline + 102 hours. The VI-VAS AUC was compared between the treatment groups within an ANCOVA model with the stratification factor duration of vertigo (≤24 hours, >24 hours before being treated) and the baseline VI-VAS as covariates. The 2 comparisons to placebo (SENS-111 at 100 mg versus placebo and SENS-111 at 200 mg versus placebo) were tested for superiority at 5% 1-sided significance level; the corresponding 90% 2-sided confidence intervals are presented.

A sensitivity analysis using the date/time of the first dose intake of the randomized IMP as the time reference for the AUC calculation was also performed. In this analysis, Baseline was defined as the last observation recorded until the time of the first dose intake. The AUC calculation was conducted using all VAS assessments between Baseline and Baseline + 102 hours. This analysis was conducted on the mITT and the PP populations, restricted to those subjects for whom the baseline standing VI-VAS based on the first IMP intake was available and ≥60 mm.

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

As a complementary analysis in order to get a better insight of the treatment effect over time, the 8 post-baseline VI-VAS scores were analyzed without replacement of missing values, using a restricted maximum likelihood-based repeated measures approach.

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	Descriptive summaries were provided where appropriate for each of the primary and secondary variables. In general, tables summarized data by treatment arms. Plasma exposure to SENS-111 was characterized by describing summary statistics of plasma concentration of SENS-111 by treatment arm and visit.
SUMMARY OF RESULTS AND CONCLUSIONS:	
Efficacy and Pharmacokinetic Results:	The following conclusions could be drawn from the efficacy and PK results of the study: • No statistically significant differences between the active treatments and placebo were shown in the vertigo intensity measured by the AUC of the VI-VAS in standing position over the 4 treatment days (8 post-baseline assessments) (ITT population: SENS-111 100 mg: 18.57, 90% confidence interval [CI]: -11.45 to 48.59, *P* = 0.8466; SENS-111 200 mg: 12.98, 90% CI: -16.38 to 42.34, *P* = 0.7677; SENS-111 pooled: 15.64, 90% CI: -10.23 to 41.51, *P* = 0.8411). In the sensitivity analysis by ANCOVA using the date/time of the first dose intake of randomized IMP as the time reference for the AUC calculation, restricted to subjects for whom the baseline standing VI-VAS based on first IMP intake was available and ≥60 mm, no statistically significant differences between the active treatments and placebo were observed in the mITT population. In a further sensitivity analysis of AUC for standing VI-VAS by mixed-effects model for repeated measures (12H to 96H), no statistically significant differences were shown. • In the analysis of the worst spontaneous vertigo intensity, the mean (SD) AUC for worst VI-VAS were comparable between the treatment groups (SENS-111 100 mg: 180.1 [67.20], SENS-111 200 mg: 170.4 [89.83], placebo: 140.8 [64.66]). The mean (SD) length of the AUC observation period was also comparable in all 3 groups (SENS-111 100 mg: 96.2 [2.60], SENS-111 200 mg: 97.0 [2.16], and placebo: 96.6 [2.79]). In the ANCOVA analysis, no statistically significant differences between the active treatments and placebo were shown. In the ANCOVA excluding subjects who received treatment related to AUV over the last 3 months prior to enrollment, no statistically significant differences between the active treatments and placebo were observed. • The mean changes from Baseline in Romberg test were comparable between the treatment groups throughout the study for the sub-scores as well as for the total score. No statistically significant difference was observed, neither at the EOS Visit (D28) (SENS-111 100 mg: -0.16, 90% CI: -0.60 to 0.28, *P* = 0.2741; SENS-111 200 mg: 0.03, 90% CI: -0.41 to 0.46, *P* = 0.5384; SENS-111 pooled: -0.06, 90% CI: -0.45 to 0.32, *P* = 0.3930) nor at the EOT Visit (D5) (SENS-111 100 mg: -0.08, 90% CI: -0.60 to 0.45, *P* = 0.4047; SENS-111 200 mg: -0.19, 90% CI: -0.72 to 0.34, *P* = 0.2752; SENS-111 pooled: -0.13, 90% CI: -0.60 to 0.33, *P* = 0.3166). • No statistically significant differences in the estimate of difference in least squares (LS) means between active treatments and placebo by ANCOVA were observed in the average and peak slow phase velocity as measured by oculography.

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- In the analysis of the AUC of NI-VAS, no statistically significant difference in LS means for active treatments versus placebo was observed (SENS-111 100 mg: 2.75, 90% CI: -25.94 to 31.44, *P* = 0.5630; SENS-111 200 mg: -0.27, 90% CI: -28.77 to 2824, *P* = 0.4938; SENS-111 pooled: 1.22, 90% CI: -23.63 to 26.07, *P* = 0.5324).
- In the Dizziness Handicap Inventory (DHI) total score and sub-scores, the mean changes from Baseline were comparable between the treatment groups at Visit 7, EOS (D28) (SENS-111 100 mg versus placebo: estimate of difference in LS means: 1.11, 90% CI: -4.22 to 6.45, *P* = 0.6358; SENS-111 200 mg versus placebo: estimate of difference in LS means: 5.80, 90% CI: 0.51 to 11.09, *P* = 0.9638; SENS-111 pooled: estimate of difference in LS means: 3.50, 90% CI: -1.23 to 8.22, *P* = 0.8896).
- At Visit 7, EOS (D28), comparable mean (SD) values were observed for the Vestibular Disorders Activities of Daily Living scale (VADL) total score (SENS-111 100 mg: 1.6 [1.14], SENS-1111 200 mg: 2.2 [1.55], placebo: 1.4 [0.86]) and sub-scores between the groups.
- The comparison of the treatment groups regarding standing VI-VAS and worst VI-VAS assessments on D28 did not suggest a trend over time.
- The time to unassisted walk was comparable between the treatment groups (SENS-111 100 mg versus placebo: hazard ratio = 0.925, 90% CI: 0.574 to 1.492, *P* = 0.6170; SENS-111 200 mg versus placebo: hazard ratio = 0.932, 90% CI: 0.575 to 1.511, *P* = 0.5933). In the analysis including the covariate stratification factor duration of vertigo, no statistically significant difference between active treatments and placebo was observed (SENS-111 100 mg versus placebo: hazard ratio = 0.906, 90% CI: 0.561 to 1.466, *P* = 0.6315; SENS-111 200 mg versus placebo: hazard ratio = 0.899, 90% CI: 0.550 to 1.470, *P* = 0.6380).
- In the safety population, the mean (SD) plasma concentration of SENS-111 was more than 2 times higher in the SENS-111 200 mg treated subjects than in those subjects treated with SENS-111 100 mg at each visit, with a high inter-subject variation.
- For the ANC endpoints, the absolute mean values of the vHIT and caloric test similarly increased in all treatment groups over time.

Safety Results: The following conclusions could be drawn from the evaluation of AEs, laboratory results, vital sign measurements, and ECG findings:

- No deaths occurred during the study. One serious AE (SAE) occurred in 1 subject (diverticular perforation) receiving 200 mg of SENS-111; it was severe and considered unlikely related to the IMP. The outcome was reported as recovered/resolved with sequelae. One subject had withdrawn from the study due to a non-serious treatment-emergent AE (TEAE) of rash, which was moderate and considered probably related to the IMP, with a reported outcome of recovering/resolving.
- Overall, the number of subjects with at least 1 TEAE among the treatment groups was comparable, with 9 subjects (25.0%) affected in the 100 mg group, 14 subjects (38.9%) in the 200 mg group, and 12 subjects (37.5%) in the placebo group.

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	• The most frequent TEAEs reported in ≥5% of subjects in either group were nervous system disorders with overall incidence of 15.4%, with headache occurring in 12.5% of the subjects overall. The system organ classes (SOCs) of gastrointestinal disorders and metabolism and nutrition disorders had an overall incidence of 5.8% each, but no single preferred term occurred in >5% of subjects. • Reported TEAEs were mostly mild or moderate in severity and self-limiting. Severe TEAEs included the single SAE reported in the study and a non-serious severe TEAE of extra dose administered experienced by 1 subject in the placebo group. This event was set to severe using the worst case scenario due to missing results of the severity assessment. • The placebo group had the highest proportion of subjects with a TEAE considered related to the IMP (6 subjects [18.8%]), followed by the group receiving 200 mg of SENS-111 (5 subjects [13.9%]). The group receiving SENS-111 at a dose of 100 mg had the lowest proportion of subjects with a TEAE considered related to the IMP (4 subjects [11.1%]). • Clinical laboratory, vital signs, and physical and neuro-otological examinations results did not signal any safety concerns.
CONCLUSIONS:	• In the present study, the 2 active treatments (SENS-111 100 mg and 200 mg) did not show efficacy as compared to placebo. The study did not meet the primary endpoint of an improvement in vertigo intensity, measured by the AUC of the VI-VAS in standing position over the 4 treatment days, with 8 post-baseline assessments. • Quality of life, as assessed by the DHI total score and sub-scores, was comparable between the treatment groups. • Since no efficacy of SENS-111 could be demonstrated in this study, the optimal dose regimen could not be established. • SENS-111 was safe and well tolerated in subjects with AUV. • No effect of SENS-111 on long-term recovery of the vestibular function could be observed. • Approximately dose-proportional increases in SENS-111 plasma exposure were seen, together with a high inter-subject variation. • No effects of SENS-111 treatment on the preliminarily health economics assessed were observed.
DATE OF THE REPORT:	12-May-2020