# CLINICAL TRIAL PROTOCOL

**STUDY COMPOUND: SENS-401**

**STUDY Number: SENS 401-201**

A two- part, randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of SENS-401 in subjects with severe or profound sudden sensorineural hearing loss.

## AUDIBLE-S

**A** study to evaluate the **U**se of SENS-401 in SSNHL **DI**sease, given **B**ID for a 28-day **LE**ngth – by **S**ensorion

Global Clinical Trial Protocol Version 4.0 dated 05 February 2021

| **Clinical Trial Protocol Version** | **Date** | **Incorporating Amendment#** | **Applicable country/countries** |
|---|---|---|---|
| 2.1 | 12 June 2018 | N/A | All countries, except Canada |
| 2.2 | 17 September 2018 | 1 (Country specific) | Canada only |
| 3.0 | 19 March 2020 | 1 (Country specific) and 2 (Global) | All countries |
| 4.0 | 05 February 2021 | 3 (Global) | All countries |

EudraCT number: 2018-000812-47

# CLINICAL TRIAL PROTOCOL APROVAL FORM

I have reviewed the protocol, entitled:

"A two- part, randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of SENS-401 in subjects with severe or profound sudden sensorineural hearing loss"

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,safety and data protection 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 reason, 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

Name:

DATE: SIGNATURE:

SPONSOR

Name:

DATE: SIGNATURE:

STUDY CONTACT LIST

For questions regarding the conduct of the trial, please contact:

**SPONSOR**
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Chief Medical Officer:

Clinical Development Director:

**PROJECT MANAGEMENT**

**DRUG SAFETY:**

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# 2 LIST OF ABBREVIATIONS

AAA: American Association of Autology
AAO-HNS: American Association of Otolaryngology-Head and Neck Surgery
ABR: Auditory brainstem response
ADRs: Adverse Drug Reactions
AE: Adverse event
ALP: Alanine phosphatase
ALT: Alanine aminotransferase
ANCOVA: Analysis covariates
ANSI: American National Standards Institute
APD: Action Potential Depolarisation
ASAT: Aspartate Transaminase
ASHA: American Speech-Language Hearing Association
ASNHL: Acute sudden neurosensorial hearing loss
AUC: Area under the curve
BID: Bis in die (twice a day)
BP: Blood Pressure
CBC: Complete blood count.
CKD-EPI creatinine equation: Chronic Kidney Disease EPIdemiology collaboration equation
Cl: Clearance
Cmax: Maximum concentration
CNS: Central nervous system
COMT: Catechol O-methyltransferase
CRF: Case report Form
CRO: Clinical research organization
CRP: C reactive protein
C-SSRS: Colombia- Suicide Severity Risk score
CSR: Clinical study report.
CTCE: Common Terminology Criteria for Adverse Events
CYP: Cytochrome
D: Day
dB: Decibel
DB: Double-blind
DDI: Drug-Drug Interaction
DPOAE: Distortion Products Otoacoustic Emissions
DMC: Data Monitoring Committee
ECG: Electrocardiogram
eCRF: electronic Case Report Form
ENT: Ear Nose Throat
F: Bioavailability
FU: Follow-up
GCT: Germ Cell Tumours
γGT: Glutamyl transferase

GLP: Good Laboratory Practice
GST: Group Sequential Test
Hb: hemoglobin
HCl: Hydrochloride
Hct: Hematocrit
HR: Heart rate
Hz: Hertz
ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC: Independent ethics committee
INN: International Non-proprietary Name
iNOS: inducible nitric oxide synthase
IP3R: Inositol Triphosphate Receptor
IRB: Institutional Review Board.
ISSHL: Idiopathic Sensory hearing loss
ITT: Intent to treat
IWRS: Interactive web response system
LLN: Lower Limit of Normal
LOAEL: Lowest observed adverse effect level
LOCF: Last observation carried forward
MA: Marketing Authorisation
MCP: monocyte chemo-attractant Protein
MedDRA: Medical Dictionary for Regulatory Activities
MHRA: Medicine and Healthcare products related Regulatory Agency
MDRD equation: Modification of Diet in Renal Disease
MRI: Magnetic resonance imaging
NCI: National Cancer Institute
NISHL: Noise induced Sensorineural hearing Loss
NOAEL: No observed adverse effect level
NRS: Numerical rating scale
OAES: Otoacoustic Emissions
OHC: Outer hair cell
PD: Pharmacodynamic
PK: Pharmacokinetic
PMDA: Pharmaceuticals and Medical Agency (Japan)
PP: Per protocol
PTA: Pure Tone Average of the hearing threshold of 3 contiguous most affected hearing frequencies identified at entry in affected ear
PTS: Permanent threshold shift
R: Randomised
ROS: Reactive oxygen species
SAE: Serious adverse event
SAP: statistical Analysis Plan
SHL: Sudden Hearing Loss
SoC: Standard of Care
SRAS: Severe Acute Respiratory Syndrome

SRT: Speech Recognition Threshold
SSNHL: Sudden Sensorineural Hearing Loss
STS: Standard threshold shift
SUSAR: Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$: Elimination half life
TEAE: Treatment-emergent adverse event.
TFI: Tinnitus functional index
$t_{Max}$: Time to Maximum concentration
TOEAE: Transient Evoked Otoacoustic Emissions
ULN: Upper Limit of Normal
WBC: White blood count
WOCBP: Woman of child-bearing potential
WRS: Word Recognition Score

# 3 CLINICAL TRIAL SUMMARY

| NAME OF COMPANY: Sensorion | NAME OF PRODUCT: SENS-401 | ACTIVE INGREDIENT: (R)-azasetron besylate |
|---|---|---|

**Study Title**

A two- part, randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of SENS-401 in subjects with severe or profound sudden sensorineural hearing loss

**Short Title: AUDIBLE-S**

**A** study to evaluate the **U**se of SENS-401 in SSNHL **DI**sease, given **BI**D for a 28-day **LE**ngth – by **S**ensorion

**Study Code Number:** SENS 401-201

**International Coordinators**

Professor Arne Ernst (Germany)

**Study Phase:** 2b/3

**Objectives**

- **Primary objective:**

To assess the efficacy of SENS-401 on hearing loss in comparison to placebo at the end of the 4-week treatment period.

- **Secondary objectives:**

To confirm the maintenance of any early efficacy on hearing loss at 12-week

To evaluate the efficacy on tinnitus

To determine the dose effect on hearing loss

To confirm the safety of SENS-401 in the studied population/dosage regimen

**Methodology/Study Design**

The study is a 2-part, multicenter, double-blind, randomised, placebo-controlled study of SENS-401 administered orally twice daily (BID for 28 days), with an 8-week follow-up. The study will be conducted according to an operational seamless design. In the first part, 2 doses of SENS-401 29 mg/BID and 43.5 mg/BID (respectively 20 mg and 30 mg free base) will be tested. In the second part, only the dose that demonstrated efficacy in Part 1 will be tested.

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The selection of the dose will be done by the DMC when all patients have completed 28 days of treatment in Part 1.

SENS-401 or placebo will be given on top of the "standard of care" oral corticosteroids under the responsibility of the Investigator.

Moreover, a rescue therapy by intra-tympanic corticosteroids could be administered from day 14 in case of non-response under the responsibility of the Investigator.

**Number of Subjects**

The total number of subjects in the study will be 301 or less, broken down as follows:

Part 1: Randomised: 111

29 mg dose group: n = 37
43.5 mg dose group: n = 37
Placebo group: n = 37

Part 2: Randomised: 190

Selected dose group: n = 95
Placebo group: n = 95

**Number of centers:** about 50 centers

**Diagnosis and Main Criteria for Inclusion**

Patients will be included if they are presenting with **sudden sensorineural hearing loss** and have met all the following inclusion criteria and no exclusion criteria:

**Inclusion criteria**

1. Male or female
2. Aged at least 18 years old
3. Patients with unilateral idiopathic sudden sensorineural hearing loss or unilateral/bilateral acute acoustic trauma leading to sudden sensorineural hearing loss defined by both:

3.1. At least 1 hearing threshold of 50 dB or more amongst the 3 most affected contiguous frequencies on pure tone audiometric air conduction testing performed 24 hours or less prior to first study treatment,

and

3.2 Mean hearing loss of 30 dB or more, averaged across the 3 most affected contiguous frequencies on pure tone audiometric air conduction testing (PTA: Pure Tone Average)

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performed 24 hours or less prior to first study treatment, compared with the unaffected contralateral ear or reference values from a pre-existing audiogram (dated less than 2 years)

4. Patients with sudden hearing loss with onset within 96 hours prior to first study drug intake.
5. Females must meet one of the following: postmenopausal defined as 12 consecutive months with no menses without an alternative medical cause, surgically sterile, abstinent; or practicing **highly** effective birth control (must agree to use 2 forms of contraception [1 of which must be a barrier method]) (Appendix 4) and willing to continue to use **highly** effective contraception for the duration of study participation and for 30 days after the final dose of study drug). Women of childbearing potential must have a negative pregnancy test at screening before the first dose of study drug is taken. Women of childbearing potential are defined as any female who has experienced menarche and who is not permanently sterile or postmenopausal.
6. Male subjects and their female partner(s) must agree to use **highly** effective contraception (must agree to use 2 forms of contraception [1 of which must be a barrier method]) (Appendix 4) for the duration of study participation and for 90 days after the final dose of study drug.
7. Signed and dated written informed consent.

**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. Bilateral idiopathic hearing loss
2. Fluctuating hearing loss
3. History of asymmetric hearing (>20dB difference between ears) to the best knowledge of the patient
4. Severe hearing loss (>90 dB) associated with unilateral (ipsilateral) complete vestibular loss
5. History of Ménière's disease, autoimmune hearing loss, radiation-induced hearing loss, acoustic neuroma (schwannoma)
6. Previous SSNHL in the affected ear within the past 6 weeks
7. History of otosclerosis, suspected perilymph fistula or membrane rupture, suspected retro-cochlear lesion, barotrauma
8. Congenital or hereditary hearing loss
9. History of severe head or neck trauma
10. Complete loss of peripheral vestibular function on the affected side

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11. Any drug-based therapy for inner ear hearing loss that is ongoing or was performed in the past 6 weeks, except oral corticosteroids
12. Any ongoing or planned concomitant medication for the treatment of tinnitus until 6 weeks after administration
13. Any therapy known as ototoxic (e.g. aminoglycosides, cisplatin, loop diuretics, quinine etc.) at the current time or in the past 6 months prior to study inclusion
14. Air-bone gap of greater than 20 dB in 3 contiguous frequencies
15. Acute chronic otitis media or otitis externa terminated less than 7 days prior to randomisation.
16. History of chronic inflammatory or suppurative ear disease or cholesteatoma,
17. Prior ear surgery of any kind (except ventilating tubes), or cochlear implants
18. Patients with moderate to severe renal impairment defined by a creatinine clearance ≤ 60 ml/min (calculated with the Cockroft-Gault formula for patients <65 years old and with CKD-EPI creatinine equation or with MDRD equation for patients ≥65 years old)
19. Treatment with triptans within the 24 hours before inclusion.
20. History of drug abuse or alcoholism within the last 2 years
21. Known or suspected ongoing active infection of HIV, Hepatitis B or C, or herpes zoster
22. Known history of, or concomitant severe hepatic, gastrointestinal, cardiovascular, respiratory, neurological (except vertigo or tinnitus), hematological, renal, dermatological or psychiatric disease or substance abuse or any condition that, in the opinion of the Investigator might interfere with the evaluation of study treatment or warrant exclusion (see list of discontinuation criteria, section 11.3.2)
23. Patients who, in the opinion of the Investigator, have any clinically relevant findings that warrant exclusion. Examples of clinically relevant problems include, but are not limited to, 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
24. Neurological disorders including stroke, demyelinating disease, brain stem or cerebellar dysfunction within the last 3 months. (In case of possible stroke of the brainstem or cerebellum, or demyelinating disease the diagnosis should have been excluded by a MRI performed in the past 48 hours)

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25. Known hypersensitivity, allergy or intolerance to the study medication or any history of severe abnormal drug reaction
26. Pregnant or breast-feeding
27. Mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing its constraints
28. Treatment with any investigational agent within 4 weeks prior to randomisation or 5 half-lives of the investigational drug (whichever is longer)
29. Prior participation in a clinical trial with SENS-401 or any past treatment with azasetron
30. 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
31. Patients with either a history of significant arrhythmia, or a history of conditions known to increase the proarrhythmic risk (e.g., congestive heart failure, long QT Syndrome, hypokalemia etc...).

**Test Product**

| | |
|---|---|
| Product name: | SENS-401 |
| Unit dose: | 14.5 mg Oral Tablet (10mg free base equivalent) |
| Regimen: | Twice daily |
| Mode/route: | Oral |

**Drug Being Tested, Dose, Method of Administration**

- 29 mg dose group: 2 tablets of 14.5 mg SENS-401, and 1 tablet of matching placebo, twice daily (morning and evening), oral route
- 43.5 mg dose group: 3 tablets of 14.5 mg SENS-401 twice daily (morning and evening), oral route
- Placebo group: 3 matching placebo tablets twice daily (morning and evening), oral route

**Duration of Treatment:** 28 days

**Non-Investigational Treatment**

**Background treatment:** There is no standardized treatment for SSNHL. However, corticosteroids are usually given to patients with SSNHL as a standard of care. Therefore, oral corticosteroids unless contra-indicated will be given to all patients. Treatment and dose to be administered will be the investigator responsibility.

**Rescue therapy:**As proposed by the American Association of Otolaryngology-Head and Neck Surgery (AAO-HNS) guidelines, in case of no hearing improvement, a rescue

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treatment consisting of an intra-tympanic administration of corticosteroids starting at the earliest on Day 14 will be permitted. The dose to be administered is not standardized as the AAO-HNS or EU do not provide any guidance. The decision to use the rescue medication, the type of corticosteroid and dose to be administered will be the investigator's responsibility.

**Criteria for Evaluation**

**Primary Endpoint**

Change in pure tone audiometry (PTA; average of the hearing threshold of 3 contiguous most affected hearing frequencies in decibels as identified at study entry) in affected ear from baseline to the end of treatment visit (Visit D28± 3).

**Secondary Endpoints**

- Change in pure tone audiometry (average of the hearing threshold of the 2 most affected hearing frequencies identified at study entry) in affected ear from baseline to the end of treatment visit (Visit D28± 3).
- Change in pure tone audiometry (the most affected hearing frequencies identified at study entry) in affected ear from baseline to the end of treatment visit (Visit D28± 3).
- Change in speech discrimination threshold from baseline to Days 28, and 84
- Frequency and severity of tinnitus at Days 7, 14, 28, and 84 assessed by numerical rating scale

**Exploratory Efficacy endpoints**

- % of patients with complete hearing recovery defined as PTA <20 dB or hearing similar to the unaffected contralateral ear.
- % of patients with marked improvement defined as PTA threshold absolute improvement > 30 dB
- % of patients with PTA > 35 dB and > 90 dB on Day 7, Day 14 and end of study visit (visit D84± 3)
- Change in PTA from baseline to Day 7, Day 14 and end of study visit (Visit D84± 3).
- % of responders (response defined as an improvement of 10dB or more in PTA)
- Word recognition score at 80 dB and 60 dB in the affected ear on Day 28 and 84.
- Relationship between time from onset of symptoms to first study drug intake and the primary endpoint
- Frequency and severity of any vertigo at day 1,7,14, 28 and 84
- Tinnitus burden based on the change in tinnitus QOL scores at day 1,7,14, 28 and 84

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- Change in biomarkers
- Change in EQ-5D-5L scores between baseline and Day 28 and 84.
- Change in DPOAE at Days 7, 14, 28, and 84 compared to baseline values
- Change in TEOAE at Days 7, 14, 28 and 84 compared to baseline values

**Safety Evaluation**

- Overall tolerability: incidence, severity and nature of adverse events and SAE throughout the study course
- Clinical chemistry and hematology parameters at baseline and on Days 7, 14, and 28
- ECG findings
- Suicidality assessment (C-SSRS)

**Pharmacokinetic evaluations**

Serum samples will be collected for pharmacokinetic (PK) analysis on Day 14 (Visit 4) and End of treatment visit (Visit 5).

**Data Monitoring Committee (DMC)**

An independent DMC will be organized to regularly evaluate the safety of SENS-401 during the study. The DMC will be regularly provided with safety data. Safety data will be provided by patient with relevant information after 30 patients have completed the study and then after 85 (±5) and 111 (±5) patients have completed Day 28 during Part 1, every 50 patients (around 25 patients/group) during Part 2, or at least once a year. The DMC will remain blinded for its evaluation but may ask for unblinding if required.

Following their risk evaluation, the DMC reserves the possibility of alerting the Sponsor in the event of observation of highly unexpected events.

During Part 1, two interim efficacy looks are planned. They will be performed by an independent statistician dedicated to the Group Sequential Test (GST). Each of these interim looks will lead to an automatically generated recommendation to the sponsor of continuing the study or of discontinuing the study for efficacy or futility respectively.

The committee will review the results and will provide further recommendation to the sponsor for stopping Part 1 for efficacy or futility or continuing Part 1 as planned, until the next look or the final analysis of Part 1. No information about these results will be communicated to investigators and the International Coordinating Investigator until the study is completed or discontinued.

The committee will be responsible for the recommendation of the dose level of SENS401 selected in Part 2. The committee will be provided with the unblinded efficacy and safety data on the primary endpoint once the sample size used for the final analysis of Part I of 111 (±5) patients randomised and will have completed the 4-week treatment. The DMC

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| will review the data provided to evaluate the benefit/risk ratio and recommend appropriate measures if needed. The DMC may also recommend to modify the sample size of the Part 2 study. | | |

**Statistical methods**

**Sample Size Calculation**

The sample size is based on the average change in PTA in dB between the baseline and week 4 in each part of the study.

***Part 1:*** A sample size of 111 patients (37 patients per treatment arm) was retained corresponding to following assumptions:

- Each comparison to placebo performed at 5% one-sided significance level (higher dose to be tested first and low dose to be tested conditionally to the high dose statistical results)
- Power of each comparison to placebo set to 75%.
- Randomisation ratio 1:1:1
- Intra-group standard deviation of 30 dB
- Difference to placebo of 15dB.
- Corresponding fixed sample size design of 105 patients (35 patients per treatment arm) inflated to 111 patients (37 patients per treatment arm) to allow the use of GST design with 3 looks (2 interim and 1 final look)

***Part 2:*** A sample size of 190 patients (95 patients per treatment arm) is retained corresponding to following assumptions:

- The comparison to placebo performed at 5% two-sided significance level
- Power of the comparison to placebo set to 90%.
- Randomisation ratio 1:1
- Intra-group standard deviation of 20 dB
- Difference to placebo of 10 dB.
- 10% dropout rate

The sample size of Part 2 will be re-estimated based on Part 1 results when available.

**Analysis sets**

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

**Main Efficacy Endpoints**

Mean changes from baseline of the hearing PTA at days 7, 14 and 28 will be analysed using a restricted maximum likelihood (REML)-based repeated measures approach. Analyses will include the categorical, fixed covariates of duration of disease and oral corticosteroids intake at baseline (stratification factors), the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline

score and baseline score-by-visit 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 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. The estimations and standard errors of the contrasts of interest will be derived from this model. The primary comparison(s) to placebo will be the ones at week 4; the comparisons to placebo at the other visits being seen as secondary.

Similar approaches will be used for the other efficacy endpoints.

**Safety endpoints**

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

Adverse events (AEs) will be coded and evaluated for severity using MedDRA and 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 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 test parameter. Number and percentage of patients presenting at least one post-baseline potentially clinically significant abnormality will be presented by treatment group for selected parameters.

Number and percentage of patients presenting at least one post-baseline potentially clinically significant ECG abnormality will be presented by treatment group for selected parameters.

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 vital sign parameter. Number and percentage of patients presenting at least one post-baseline potentially clinically significant abnormality will be presented by treatment group for selected parameters.

Data from physical exams will be presented in the data listings.

**Study Timelines**

Duration of clinical phase: 12 weeks corresponding to 28 days of investigational product (IP) + 8 weeks of follow-up without IP.

**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-401, 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

| **Phase** | **Screening** | **Double-blind Treatment** | | | | **Follow-Up** |
|---|---|---|---|---|---|---|
| Day | Day-4 to Day 1 | **Inclusion** Day 1 | Day 7 (±2) | Day 14 (±2) | **End of treatment** Day 28 (±3) | **End of study** Day 84 (±3) |
| **Study Visits** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** |
| Informed Consent | X | | | | | |
| Inclusion and Exclusion Criteria | X | X | | | | |
| Demographic data | X | | | | | |
| Medical/Surgical/Otologic History | X | | | | | |
| Otoscopy and tympanometry | X | X | X | X | X | X |
| **Treatment** | | | | | | |
| Randomisation (IWRS) | | X | | | | |
| Study drug administration | | ← | — | — | → | |
| Study drug Compliance[1] | | | X | X | X | |
| Oral Corticosteroids Compliance[1,2] | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X |

1 IP (dose, date, time) and oral corticosteroids intake will be captured daily on a patient diary (with the exception of the IP dose at Visit 1).
2 All patients will receive oral corticosteroids, unless contra-indicated. The type, dose and duration will be at the discretion of the investigator.

| Day | Day-4 to Day 1 | Inclusion Day 1 | Day 7 (±2) | Day 14 (±2) | End of treatment Day 28 (±3) | End of study Day 84 (±3) |
|---|---|---|---|---|---|---|
| **Study Visits** | V1 | V2 | V3 | V4 | V5 | V6 |
| **Safety** | | | | | | |
| Physical Examination | X | | | | X | X |
| Vital signs | X | X | X | X | X | X |
| 12 lead-ECG | | X | X | X | X | |
| Laboratory blood test | X | | | X | X | |
| Pregnancy test (WOCBP)[3] | X | | | X | X | X |
| Adverse events | ← | — | — | — | — | → |
| Suicidality assessment (C-SSRS) | | X | X | X | X | |
| **Efficacy** | | | | | | |
| Pure Tone Audiometry (air and bone) | X[4] | X[5] | X | X | X | X |
| DPOAE / TOEAE (optional) | | X | X | X | X | X |
| Word Recognition Score | | X | X | X | X | X |
| Speech Recognition Threshold | | X | X | X | X | X |
| Vertigo Severity (NRS) | | X | X | X | X | X |
| Tinnitus Severity (NRS)[6] | | X | X | X | X | X |
| QoL: 5EQ-5D-5L; TFI | | X | X | X | X | X |

3 Pregnancy test will be urinary test (or blood test if preferred). In case of positive urinary test, a blood test will be performed for confirmation.

4 Pure tone audiometry performed within 24 hours prior to the screening visit is valid for screening.

5 Baseline Pure tone audiometry should be performed **at site**, **no more than 24 hours before the first study drug intake**. If longer, it should be repeated for confirmation
If a Pure tone audiometry has been performed at the study site for the screening visit within 24 hours prior to first study dug intake, there is no need to repeat it.

6 In addition, to the record on the e-CRF at each study visit, the patients will be given a diary to record the presence and the severity of the tinnitus on a daily basis during the first 14 days of treatment.

| **Day** | Day-3 to Day 1 | Inclusion Day 1 | Day 7 (±2) | Day 14 (±2) | End of treatment Day 28 (±3) | End of study Day 84 (±3) |
|---|---|---|---|---|---|---|
| **Study Visits** | V1 | V2 | V3 | V4 | V5 | V6 |
| **Pharmacokinetics/Biomarker** | | | | | | |
| Plasma samples for drug concentration | | | | X | X | |
| Serum sample: Prestin | | X[7] | | X | X | |

7 Serum sample for baseline prestin concentration measure will be taken before study drug intake (either at inclusion visit or screening visit)

# 5 INTRODUCTION AND RATIONALE

## 5.1 Sudden sensorineural hearing loss

Sudden hearing loss (SHL) is defined as a rapid-onset, occurring over a 72-hour period, of a subjective sensation of hearing impairment in one or both ears.

Sudden sensorineural hearing loss (SSNHL) is a subset of SHL; sensorineural in nature it is diagnosed by audiometric criteria that include (A) abnormality of the cochlea, auditory nerve, or other aspects of central auditory perception or processing and (B) a decrease in hearing of more than 30 decibels (dB), affecting at least 3 consecutive contiguous test frequencies on pure-tone audiogram (47, 49).

Based on American Speech-Language-Hearing Association criteria (ASHA), the hearing loss can be slight to profound, with corresponding grades of hearing impairment of 16 to 25 dB (slight), 26 to 40 dB (mild), 41 to 55 dB (moderate), 56 to 70 dB (moderately severe), 71 to 90 dB (severe), or > 91 dB (profound). Because premorbid audiometry is generally unavailable, hearing loss is defined as related to the opposite ear's thresholds.

The most commonly reported **causes of SSNHL** include infectious and otologic diseases (12.8% and 4.7%, respectively); **trauma, including noise-induced**, barotrauma or head trauma (4.2%); vascular/hematologic (2.8%); neoplastic (2.3%); and other (2.2%). However, 71% of cases report an unknown **(idiopathic)** cause (16).

A maximum of 32% to 65% of cases of SSNHL may recover spontaneously. Clinical experience indicates that even this recovery rate may be an overestimation. Prognosis for recovery is dependent on a number of factors, including patient age, presence of vestibular symptoms at onset, degree of hearing loss, audiometric configuration, co-morbidities (hypertension, diabetes) and time between onset of hearing loss and treatment (15) (41) (58) (21) (23) (27).

SSNHL is a serious and debilitating condition. Hearing loss adversely affects communication, speech perception in noisy environments, and social interaction, substantiating that unilateral deafness is a serious disability (59).. Disorientation and confusion from the inability to localize sound may put patients at risk for accidents and hearing loss is associated with significantly increased odds of falling in older adults (27). A psychosocial impact was reported in almost 75% of patients who had even mild unilateral hearing loss, and feeling frustrated, upset, and left out were commonly reported (38). Patients suffering from SSNHL can also experience tinnitus and/or vertigo that they consider frightening, debilitating, and negatively impacting their QoL (14) (17) (37).

SSNHL is a rare condition with an average total annual incidence rate of 4 to 160 per 100,000 and approximately 66,600 new cases reported each year in the United States. The incidence increased with increasing age, ranging from 11 per 100,000 for patients younger than 18 years to 77 per 100,000 for patients 65 years and older (3)(39).

There is currently no treatment to improve or facilitate full, or even partial, recovery of hearing and/or symptoms of SSNHL, regardless of the cause. However, a few registered compound that treat symptoms such as vertigo or tinnitus may be associated to SSNHL.

Therefore, the treatment of SSNHL remains somewhat controversial. It is widely variable and often regionally specific. The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) has issued in 2012 clinical practices guidelines for the management of SSNHL (49). No European medical society has published clinical guidelines.

In clinical practice, the most commonly used off-label treatment is corticosteroids (60) administered either systemically and/or intratympanically (44). A large number of other treatments such as antivirals, antibiotics, diuretics, vasodilators, osmotic agents, plasma expanders, anticoagulants, mineral supplements, and hyperbaric oxygen or carbon dioxide–rich gases, among others, have been used and/or evaluated without consistent success (45,61).). Recent meta-analysis evaluating the efficacy and safety of medical interventions for the treatment of SSNHL have not identified effective therapy (18, 19, 32, 33, 20;57).

Cochlear implant is an invasive procedure and is not a treatment of SSNHL. Hearing aids may be used after SSNHL in the absence of recovery but they are not useful in the acute episode.

Some cases of noise-induced SSNHL can be prevented by using hearing protection but others, such as unexpected exposure to gunshots and explosives, are not preventable (13). For military personnel or police officers, exposure to loud noises during training and missions are inevitable. In situations such as military operations, hearing is a vital asset during training and military operations and the need to communicate is more important than wearing protection (63)

### 5.2 Physiopathology of SSNHL

As specified above, SSHNL is usually idiopathic. As such, it is not predictable and cannot be reproduced in animal models to determine its pathophysiology and histopathology. It is therefore difficult to identify pathways and therapeutic targets for SSHNL. In order to tackle this issue, models of noise induced hearing loss (NIHL) have been developed in animals. They are considered as reproducing the hearing loss occurring in man after an acute exposure to noise. They are the most reproducible, well-established, commonly used models and are the only available translational tools for research and development of new therapies for SSNHL. They are used to evaluate mechanisms and efficacy of drug product candidates for the treatment of SSNHL.

Noise levels are measured as sound intensity (0 to over 180 dB). Levels 90 to 100 dB over several hours or sudden levels 115 dB can cause damage to the human ear (5). When exposed to noise, the ear protects itself by vasoconstriction, which reduces the blood supply to the cochlea's organ of Corti, located in the inner ear (54).). Insult to hair cells, neurons, and/or synapses in the organ of Corti causes a decrease in the ear's sensitivity level, and a temporary or permanent shift in hearing threshold occurs (4, 30).

Sensorineural hearing loss is caused by death of the auditory hair cells in the cochlea and the degeneration of their afferent innervation (1). In mammals, these cells are produced only during embryonic development (46) and do not regenerate postnatally (51). Therefore, the loss of auditory hair cells is an irreversible event that can cumulatively result in profound hearing losses and eventually total deafness. Hair cell death following environmental stress has been proven to occur via both necrosis and programmed cell death 56, (56 65, 22).

SSNHL natural history is characterized by frequent partial or complete hearing recovery because of cellular defenses and intrinsic repair mechanisms such as neo-synaptogenesis (43). Recent animal data suggest that slow degeneration of spiral ganglion cells and delayed hearing loss may occur even despite complete short-term recovery.

In noise-induced animal studies of SSNHL, cellular mechanisms such as intense metabolic stress and damage to many components of the cochlea, including inner and outer hair cells, stereocilia, supporting cells, neurons, fibrocytes, and spiral ganglion neurons are involved (56, 34). Molecular mechanisms, such as calcineurin activation, inflammatory cell infiltration, glutamate excitotoxicity, and/or oxidative stress have been incriminated (35, 43, 36).

Calcineurin is a $Ca^{(2+)}$/calmodulin -dependent protein phosphatase, expressed in sensorineural tissue. Calcineurin is activated after noise-induced trauma to the inner ear and can activate mitochondrial-mediated cell death pathways in outer hair cells within the cochlea. It has been shown that calcineurin inhibitors are effective at reducing or preventing hair cell damage in animals (36, 34,55), and are protective against noise induced cochlear injury (12).

Calcineurin inhibition directly targets the pathological mechanisms of sensory hair cell death and degeneration of the stria vascularis that are key pathways in noise NIHL. Calcineurin inhibition is therefore expected to reduce cochlear damage and thus limit the intensity of the hearing loss.

## 5.3 SENS-401

The active ingredient in SENS-401 is the (R)-enantiomer of the racemic mixture of (R/S) azasetron, a serotonin type 3 (5-$HT_3$) receptor antagonist marketed in Japan as Serotone®. Serotone® is approved for the treatment of nausea and vomiting in patients undergoing chemotherapy.

### 5.3.1 In vitro pharmacology results

Non-clinical pharmacology studies have shown SENS-401 to be a 5-$HT_3$R antagonist as R/S azasetron, (Serotone®). In addition, R/S azasetron, has been shown to possess calcineurin inhibition properties with an IC50 of about 100 nM (35 ng/mL).

Calcineurin is a $Ca^{(2+)}$/calmodulin activated serine/threonine protein phosphatase expressed in sensorineural tissue. Pathological activation of calcineurin by excessive calcium influx calcineurin activation (24) (49) (64) leads to:

- increased nuclear NFAT translocation resulting in increased oxidative stress through iNOS upregulation
- increased dephosphorylation of cofilin, leading to actin depolymerization resulting in synaptic swelling/uncoupling, neurite retraction and structural degeneration
- increased mitochondrial translocation of pro-apoptotic BAD (Bcl-2-associated death promoter) from the cytosol, resulting in the mitochondrial release of cytochrome C and other signalling factors for activation cellular apoptotic cascades.

A $5HT_3$ antagonist (tropisetron) was demonstrated to target the $Ca^{(2+)}$/calmodulin-dependent protein phosphatase 2B/calcineurin, and to inhibit the transcriptional NFAT and AP-1 activation, and IL-2 production induced by overexpression of an active form of the phosphatase calcineurin (21).

It was expected that the blockade of $5HT_3$ and inhibition of calcineurin by SENS-401 would directly target the mechanisms of SSNHL by reducing the impact of excessive calcium influx, limiting increased oxidative stress and countering the activation of pro-apoptotic cascades.

Based on this mechanism of action, the activity of SENS-401 was evaluated in the rat models of the treatment of noise induced hearing loss, in the prevention of cisplatin induced hearing loss and in the treatment of unilateral vestibular dysfunction.

### 5.3.2 SENS-401 in vivo pharmacology

In animal model (rats) of severe acoustic trauma, initial studies showed a treatment effect from 6.6 mg/kg oral, SENS-401 significantly improving auditory brainstem response (ABR) thresholds and DPOAE amplitudes and reducing the average hearing loss. Improvement in ABR threshold shifts and DPOAE amplitudes in animal models of NIHL are considered to be predictive of a protective and potentially curative effect on SSNHL in patients.

The improvement was shown to be dose dependent, and time dependent. The effect was shown to be present when SENS-401 was given up to 96 hours after the insult.

Also, the efficacy of SENS-401 was confirmed in a rat model of prevention of cisplatin induced hearing loss and demonstrated to start at doses as low as of 6.6 mg/kg (4.55 mg/kg free base equivalent) and to increase dose-dependently to the highest tested dose of 26.4 mg/kg.

In both models, SENS-401 reduced the number of hair cell loss as compared to placebo.

### 5.3.3 SENS-401 toxicology

SENS-401 has been administered to rats and dogs for 1 month. The safety was good with a NOAEL dose > 25 mg/kg/day (free-base equivalent) in the dog, corresponding to Cmax >3200ng/mL and, AUClast >10800ng.h/mL. In the rat, the NOAEL was >157 mg/kg/day (free-base equivalent), corresponding to a Cmax > 9800 ng/mL, AUClast > 80500 ng.h/mL. In a telemetry study, SENS-401 was shown to slightly reduce blood pressure resulting in modest dose independent increases in heart rate and then QT interval (<30ms) with no relationship with dose or concentrations. No target organ has been identified.

As SENS-401 is a substrate of MDR1 and BCRP transporters, drugs that are inhibitors of these are listed as prohibited. In *in vitro* experiments using recombinant enzymes, some CYP2B6 inhibition was observed at 25 µM (approximately 37 %) which did not increase at 100 µM (approximately 24 %). This level of inhibition at a very high concentration is unlikely to cause any interactions clinically. Therefore, no restrictions are proposed in the protocol.

Patients will be advised to avoid skin exposure to strong sunlight and to wear sunglasses in bright sunlight for the duration of the study and for 1 week after the last dose.

No specific safety concern was identified from the 3-month oral toxicity studies, and reprotoxicology studies performed with the racemic mixture. Genotoxicity studies were negative.

### 5.3.4 SENS-401 clinical data

In human, a phase 1 study conducted in 36 healthy adult volunteers, confirmed SENS-401 to be well tolerated at doses up to 43.5 mg bid for 7 days. In particular no CNS, cardiovascular (QT prolongation) or gastrointestinal (constipation) event that is usually observed with 5-$HT_3$R antagonists was observed. The PK profile was as expected and linear with dose. Extensive safety information available for the racemate mixture did not identify specific safety concern. All available information on SENS-401 is included in the Investigator Brochure

## 5.4 Risk Benefit Assessment

### 5.4.1 Study Rationale

There is currently no approved oral treatment for SSNHL. The pharmacology and the animal experiments conducted in animal models suggest that SENS-401 is a candidate compound that may be beneficial in this condition that can affect the patient's life beyond the acute episode on the consequences of hearing loss and accompanying tinnitus.

SENS-401 was selected for clinical development in patients with SSNHL based on the exposure to SENS-401 in plasma and inner ear of rats, the ability of SENS-401 to significantly reduce hearing loss in the NIHL animal model, and the anticipated effect of SENS401 to inhibit calcineurin activation, without the severe side-effects of currently approved, specific calcineurin inhibitors (such as cyclosporine or tacrolimus).

The racemic compound azasetron is marketed for years in Japan and other countries (China, Argentina and Korea). To our knowledge, no regulatory actions have been taken on Serotone® for safety or efficacy reasons.

SENS-401 possesses 5-$HT_3$ antagonist properties. The main adverse events of this therapeutic class are constipation and abdominal pain. They are usually mild or moderate and will reasonably not prevent the use of SENS-401 in the treatment of SSNHL, a severe, debilitating disease. Furthermore, the oral administration is easy and non-invasive. SENS-401 was safely administered during preclinical toxicology studies as well as during the Phase 1 study up to the 43.5mg twice daily for 7 days. There is a large post marketing safety experience with the racemate formulation in Japan.

Pure tone audiometry is a very-well standardized scientific subjective method to assess the hearing capacities in patients suffering from SSNHL. It can be completed by several other methods such as speech audiometry, otoacoustic emissions (OAE) (used also in animal models) and various scales for tinnitus assessments as proposed to be used in the present study.

The biological plausibility and the satisfactory safety profile of SENS-401 as well as a complete set of validated methods for endpoints assessment form the basis of the present study rationale in order to establish the scientific basis for a first oral safe and efficacious treatment of SSNHL.

### 5.4.2 Dose selection

The dose selection of SENS-401 was based on dose and allometric scaling including pharmacokinetics obtained from animal pharmacology models and human pharmacokinetic.

Calcineurin is inhibited by azasetron with an $IC_{50}$ at 100nM (35 ng/ml). In rat models of cisplatin induced ototoxicity and noise induced ototoxicity, SENS-401 was shown to be effective from 6,6mg/kg, corresponding to $C_{max}$=76ng/ml and $AUC_{0\text{-}last}$=331ng.h/ml.

Assuming the same distribution in human and rat for the inner ear and perilymph exposure, it is considered that SENS-401 43.5 mg (30mg free base) BID will provide concentration that demonstrated activity in rats (between $C_{min}$=43,3ng/ml and $C_{max}$=120ng/ml).

A lower dose 29mg BID will also be tested to assess the concentration effect of SENS-401. The mean concentration at this dose (between $C_{min}$-$C_{max}$=21,5-59,9 ng/ml) is in the range of the $IC_{50}$ in vitro, and the exposure (AUC) in the range of the rat SENS-401 exposure at active dose.

The treatment duration is based on the oxidative stress induced by acoustic trauma reported to last 10-15 days (61).).).). Recent publications have shown that contrary to existing dogma, noise can cause ongoing changes in cochlear structure and function long after it has ceased.

### 5.4.3 Conclusion

The pharmacology and pharmacokinetic results suggest that SENS-401 29mg BID and 43 mg BID for 4 weeks might be effective in patients presenting with SSNHL. The phase 1 results and the extent of exposure with the marketed R/S azasetron (Serotone®) provides reassurance that SENS-401 can be administered safely to patients presenting with SSNHL.

# 6 STUDY OBJECTIVES AND END-POINTS

## 6.1 Study Objectives

### 6.1.1 Primary Objective

To confirm the efficacy of SENS-401 on hearing loss in comparison to placebo after a 4-week treatment

### 6.1.2 Secondary objectives

- To confirm the maintenance of any early efficacy on hearing loss at 12-week
- To evaluate the efficacy on SSNHL related-tinnitus
- To determine the dose effect on hearing loss
- To confirm the safety of SENS-401 in the studied population/dosage regimen

## 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 endpoint

The primary endpoint is the change in pure tone audiometry (PTA; average of the hearing threshold of 3 contiguous most affected hearing frequencies in decibels as identified at study entry) in the affected ear from baseline to the end of treatment visit (Visit D28± 3).

### 6.2.2 Secondary efficacy endpoints

- Change in pure tone audiometry (average of the hearing threshold of the 2 most affected hearing frequencies identified at study entry) in affected ear from baseline to the end of treatment visit (Visit D28± 3).
- Change in pure tone audiometry (the most affected hearing frequencies identified at study entry) in affected ear from baseline to the end of treatment visit (Visit D28± 3).
- Change in speech discrimination threshold from baseline to Days 28, and 84
- Frequency and severity of tinnitus at Days 7, 14, 28 and 84

### 6.2.3 Exploratory efficacy endpoints

- % of patients with complete hearing recovery defined as PTA <20 dB
- % of patients with marked improvement defined as PTA absolute improvement > 30 dB
- % of patients with air PTA> 35 dB and > 90 dB on Day 7, Day 14 and end of study visit (visit D84± 3).
- Change in PTA from baseline to Day 7, Day 14 and end of study visit (Visit D84± 3).
- % of responders (response is defined as an improvement of 10dB or more in PTA).
- Word recognition score at 80 dB and 60 dB in the affected ear on Day 28 and 84.
- Relationship between time of onset of symptoms to first study drug intake and the primary endpoint
- Frequency and severity of any vertigo at days 7, 14, 28 and 84

- Tinnitus burden based on the change in tinnitus QOL scores at days 7, 14, 28 and 84
- Change in biomarkers
- Change in EQ-5D-5L scores between baseline and Day 28 and 84.
- Change in DPOAE at Days 7, 14, 28, and 84 compared to baseline values
- Change in TEOAE at Days 7, 14, 28 and 84 compared to baseline values

### 6.2.4 Safety endpoints

- Overall tolerability: incidence, severity and nature of adverse events and SAE throughout the study course
- Clinical chemistry and hematology parameters
- ECG findings
- Suicidality assessment using C-SSRS (Colombia- Suicide Severity Risk score)

### 6.2.5 Pharmacokinetics

- SENS-401 pharmacokinetic parameters

# 7 STUDY DESIGN

## 7.1 Description of the protocol

This is a double-blind, randomised, placebo-controlled, international study. The study will assess the efficacy and safety of orally administered SENS-401 in patients suffering from sudden sensorineural hearing loss (SSNHL).

Patients will be included if they are presenting with sudden hearing loss with onset 96 hours or less, ago. Based on inclusion/exclusion criteria, most patients will present with idiopathic or noise induced SSNHL. The screening evaluation including ear examination with otoscopic and tympanometric examination, will confirm the diagnosis and no exclusion criteria from past medical/surgical or otologic history, concomitant treatments, laboratory tests or other concomitant diseases. The duration of the disease will be calculated from the reporting time onset of hearing loss. Eligible patients will undergo evaluations including audiometric tests (pure tone audiometry) to confirm the eligibility.

Patients will be randomised to receive one of the treatments according to the relevant randomisation list (non-ancillary study sites and ancillary study sites) . Audiometric tests, speech audiometry, numerical rating scales and questionnaires will be also performed before the first intake of the investigational drug at the investigational site. The randomisation will be further stratified according to the duration of the hearing loss (≥ 24hours, or < 24 hours) and the intake of corticosteroids.

Patients will be requested to attend 4 additional visits when otologic examination and audiometric tests and speech audiometry will be performed on day 7(± 2) and 14 (±2), at the end of treatment visit on day 28(±3), and at the follow-up visit (the end of the study visit) on Day 84 (±3).

Patients will be followed for adverse events throughout the study. Inquiry about potential untoward events will be done at every on-site visit.

Safety parameters will include routine blood tests (complete blood count, chemistry, liver function tests and lipid profile), pregnancy tests (if applicable), cardiac evaluation by ECG, physical exams including neurological, otologic examination, tympanometry and vital signs (blood pressure, heart rate and body temperature).

There is no standardized treatment for SSNHL. However, oral corticosteroids are often given to the patients with SSNHL as a standard of care. Oral corticosteroids will be administered to all patients (unless specific contra indication). The treatment and dose to be administered will be the investigator responsibility, and pre-specified at each site.

As proposed by the AAO-HNS guidelines, a rescue treatment consisting of an intra-tympanic administration of corticosteroids after randomisation will be permitted from Day 14 to patients who have no hearing improvement (see §9.2). The decision to use the rescue treatment, the type of corticosteroid and dosing regimen will be the investigator's responsibility.

## 7.2 Study design

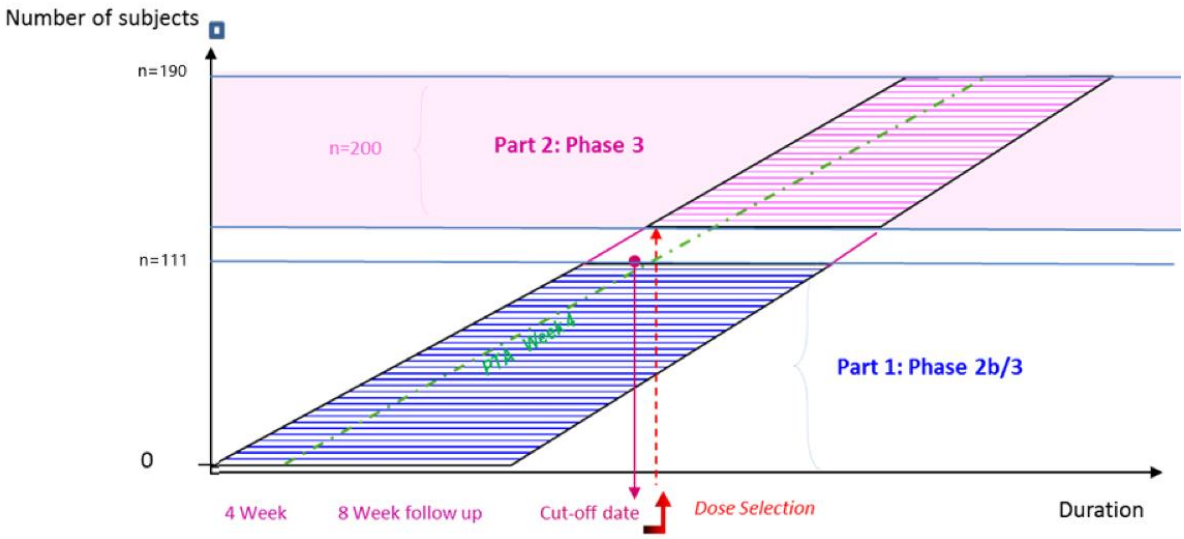
The study will be conducted with an operational seamless design and will consist of 2 separate parts:

- Part 1 is a double-blind randomised placebo-controlled Phase 2b/3 study of 28 days of treatment that will include 3 arms (2 active doses: SENS-401 29 mg and SENS-401 43.5

mg and one placebo) with an 8-week follow-up. The primary end point of Part 1 will be the change in PTA at 28 days. At the conclusion of Part 1 treatment, the data for patients enrolled in this part of the study will be unblinded by the DMC for the purposes of analysis and the dose to be tested in the confirmatory part (Part 2) will be proposed by the DMC. Patients included in Part 1 will be completely separated from patients included in Part 2.

- Part 2 is a phase 3 study. This study will be a double blind randomised placebo controlled study of 28 days of treatment that will include 2 arms with an 8-week follow-up. SENS-401 dose, either 43.5 mg or 29 mg (selected after completion of Part 1) will be tested versus placebo.

Figure 1 - Operational Seamless Design




The principle of the operational design is to continue recruitment without interruption successively into Part 1, and Part 2, according to the following steps:

1. Patients will be randomised in 3 treatment arms in Part 1 (Placebo, SENS-401 29mg, SENS-401 43.5mg). A total of 111 subjects (37/treatment arm) will be randomised.
2. The Part 1 data will be unblinded after 111 patients have been randomised in Part 1 and have completed the end of treatment visit (28 days).
3. As soon as the dose is selected for Part 2, new patients will be randomised to 2 arms (SENS-401 selected dose and placebo). No new patients will be randomised to SENS-401 non-selected dose.

The SENS-401 dose to be tested in Part 2 will be identified by the DMC using the unblinded data from Part 1. The rationale will be based on the benefit/risk at each dose. PTA at 28 days will be considered for efficacy. This committee will be independent from the sponsor. The final dose and sample size will be submitted for approval to competent authorities prior to the pivotal part start.

Each part will be analysed separately. Part 1 will be fully analyzed when all patients (n= 111) have completed the study. Part 2 efficacy analysis will be based on data from all patients who have entered into Part 2 and have been randomised to either placebo or the selected active dose (n=190).

### 7.3 Independent Review Procedures

An external data monitoring committee (DMC), consisting of two or more physicians and a statistician, 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, as well as the efficacy (see section 12.8.1).

During Part 1, two interim efficacy looks are planned. They will be performed by an independent statistician dedicated to the efficacy analyses according to a Group Sequential Test (GST) design. Each of these interim looks will lead to an automatically generated recommendation to the sponsor of continuing the study or of discontinuing the study for efficacy or futility respectively.

The committee will review the results and will eprovide further recommendation to the sponsor for stopping Part 1 for efficacy, futility or continuing as planned until the next look or the final analysis of Part 1.. No information about these results will be communicated to investigators and the International Coordinating Investigators until the study is completed or discontinued.

The committee will be responsible for selecting the active dose to be tested in Part 2. The committee will be provided with the unblinded efficacy and safety data on the primary end-point when 111 patients randomised to Part 1 have completed the 4-week treatment. The DMC will review the safety information together with the efficacy data to decide on the benefit/risk and recommend appropriate measures if needed. The DMC may also recommend to modify the sample size of the Part 2 study.

### 7.4 Study diagram

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

**Part 1**

The study diagram is presented in **Erreur ! Source du renvoi introuvable.**.

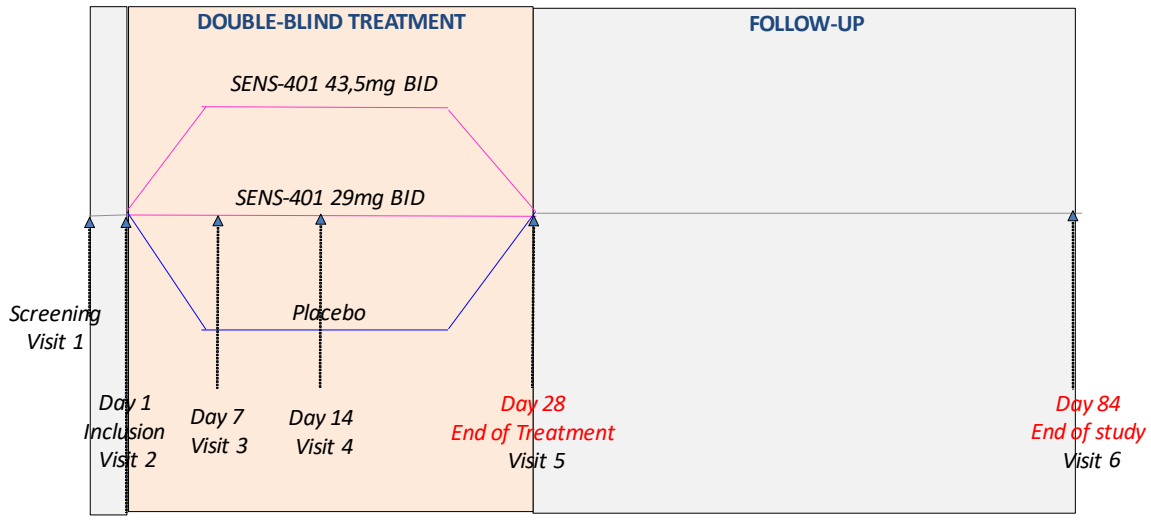



Figure 2: Part 1 and Part 2 (until dose selection) Study Diagram

Until the dose selection, the study diagram will be similar to Part 1 (see **Erreur ! Source du renvoi introuvable.**).

**Part 2**

After the dose selection, the study diagram is as follows (see Figure 3):

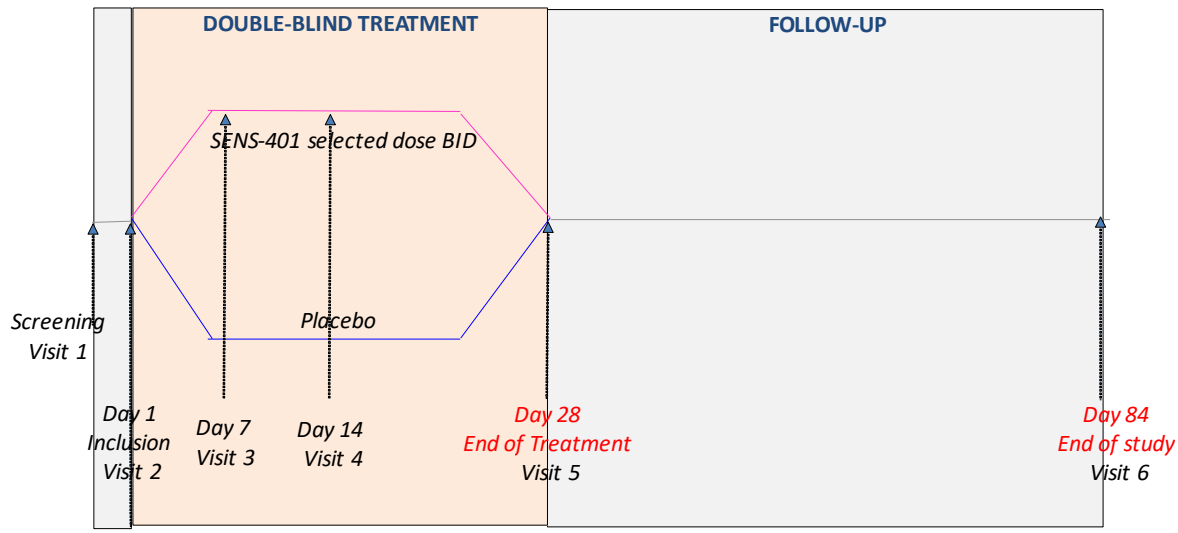



Figure 3: Part 2 (after dose selection) Study diagram

## 7.5 Number of subjects and duration of study participation

It is planned to enroll a total of 301 or less patients in the study.

Part 1: 111 patients will be enrolled (37 in the placebo arm; 37 in SENS-401 29mg arm, 37 in SENS-401 43.5mg arm)

Part 2: 190 patients will be enrolled (95 in the placebo arm; 95 in selected-dose SENS-401 arm; and approximately 10 in the non-selected dose SENS-401 arm)

Each patient's participation in the study will be 12 weeks:

- 1 to 4 days screening
- 28 days of double blind treatment
- A follow up with no investigational product until 84 Days after inclusion.

### 7.6 Determination of end of clinical trial (all patients)

The first part of the study will be considered complete when all patients randomised in Part 1 have completed all the scheduled procedures as described in the flow chart (Section 4).
Any withdrawal from treatment during the 28-day treatment period will be considered as treatment discontinuation.

The end of trial will be considered after the last subject last visit.

# 8 INCLUSION AND EXCLUSION CRITERIA

Patients will be included if they are presenting with unilateral sudden sensorineural hearing loss (noise induced or idiopathic) and have met all the following inclusion criteria and no exclusion criteria:

## 8.1 Inclusion criteria

1. Male or female
2. Aged at least 18 years old
3. Patients with unilateral idiopathic sudden sensorineural hearing loss or unilateral/bilateral acute acoustic trauma leading to SSNHL defined by both:

3.1. At least 1 hearing threshold of 50 dB or more among the 3 most affected contiguous frequencies on pure tone audiometric air conduction testing performed 24 hours or less prior to first study treatment), and

3.2. Mean hearing loss of 30 dB or more, averaged across the 3 most affected contiguous frequencies on pure tone audiometric air conduction testing (PTA: Pure Tone Average) performed 24 hours or less prior to first study treatment), compared with the unaffected contralateral ear or reference values from a pre-existing audiogram (dated less than 2 years)

4. Patients with sudden hearing loss with onset within 96 hours prior to prior to first study drug intake.
5. Females must meet 1 of the following: Postmenopausal defined as 12 consecutive months with no menses without an alternative medical cause or Surgically sterile or Abstinent or Practicing **highly** effective birth control (must agree to use 2 forms of contraception [1 of which must be a barrier method]) (Appendix 4) and willing to continue to use **highly** effective contraception for the duration of study participation and for 30 days after the final dose of study drug). Women of childbearing potential must have a negative pregnancy test at screening before the first dose of study drug is taken. Women of childbearing potential are defined as any female who has experienced menarche and who is not permanently sterile or postmenopausal.
6. Male subjects and their female partner(s) must agree to use highly effective contraception (must agree to use 2 forms of contraception [1 of which must be a barrier method]) (Appendix 4) for the duration of study participation and for 90 days after the final dose of study drug.
7. 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. Bilateral idiopathic hearing loss
2. Fluctuating hearing loss
3. History of asymmetric hearing (>20dB difference between ears) to the best knowledge of the patient
4. Severe hearing loss (>90 dB) associated with unilateral (ipsilateral) complete vestibular loss.

5. History of Ménière's disease, autoimmune hearing loss, radiation-induced hearing loss, acoustic neuroma (schwannoma)
6. Previous SSNHL in the affected ear within the past 6 weeks
7. History of otosclerosis, suspected perilymph fistula or membrane rupture, suspected retro-cochlear lesion, barotrauma
8. Congenital or hereditary hearing loss
9. History of severe head or neck trauma
10. Complete loss of peripheral vestibular function on the affected side
11. Any drug-based therapy for inner ear hearing loss that is ongoing or was performed over the past 6 weeks (except oral corticosteroids)
12. Any ongoing or planned concomitant medication for the treatment of tinnitus until 6 weeks after administration.
13. Any therapy known as ototoxic (e.g. aminoglycosides, cisplatin, loop diuretics, quinine etc.) at the current time or in the past 6 months prior to study inclusion.
14. Air-bone gap of greater than 20 dB in 3 contiguous frequencies
15. Acute chronic otitis media or otitis externa terminated less than 7 days prior to randomisation.
16. History of chronic inflammatory or suppurative ear disease or cholesteatoma
17. Prior ear surgery of any kind (except ventilating tubes), or cochlear implants
18. Patients with moderate to severe renal impairment defined by a creatinine clearance ≤ 60 ml/min (calculated with the Cockroft-Gault formula for patients <65 years old and with CKD-EPI creatinine equation or with MDRD equation for patients ≥65 years old)
19. Treatment with triptans in the 24 hours before inclusion.
20. History of drug abuse or alcoholism within the last 2 years
21. Known or suspected ongoing active infection of HIV, Hepatitis B or C, or herpes zoster
22. Known history of, or concomitant severe hepatic, gastrointestinal, cardiovascular, respiratory, neurological (except vertigo or tinnitus), hematological, renal, dermatological or psychiatric disease or substance abuse or any condition that, in the opinion of the Investigator might interfere with the evaluation of study treatment or warrant exclusion (see list of discontinuation criteria, section 11.3.2)
23. Patients who, in the opinion of the investigator, have any clinically relevant findings that warrant exclusion. Examples of clinically relevant problems include, but are not limited to, 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
24. Neurological disorders including stroke, demyelinating disease, brain stem or cerebellar dysfunction within the last 3 months. (In case of possible stroke of the brainstem or cerebellum, or demyelinating disease the diagnosis should have been excluded by a MRI performed in the past 48 hours)

25. Known hypersensitivity, allergy or intolerance to the study medication or any history of severe abnormal drug reaction
26. Pregnant or breast-feeding
27. Mentally unable to understand the nature, objectives and possible consequences of the trial, or refusing its constraints
28. Treatment with any investigational agent within 4 weeks prior to randomisation or 5 half-lives of the investigational drug (whichever is longer)
29. Prior participation in a clinical trial with SENS-401 or any past treatment with azasetron.
30. 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.
31. Patients with either a history of significant arrhythmia, or a history of conditions known to increase the proarrhythmic risk (e.g., congestive heart failure, long QT Syndrome, hypokalemia etc...).

# 9 TREATMENT

## 9.1 Investigational Product

SENS-401 14.5 mg tablets (10 mg free base), with a matching placebo

Doses in Part 1:

- 29 mg dose group: 2 tablets of 14.5 mg SENS-401 and 1 tablet of matching placebo twice daily (morning and evening), oral route
- 43.5 mg dose group: 3 tablets of 14.5 mg SENS-401 twice daily (morning and evening), oral route
- Placebo group: 3 matching placebo tablets twice daily (morning and evening), oral route

Doses in Part 2:

- 29 mg dose group: 2 tablets of 14.5 mg SENS-401 and 1 tablet of matching placebo, twice daily (morning and evening), oral route Depending upon the final dose selected, if this dose is the non-selected dose, it will be stopped immediately after the decision is taken
- 43.5 mg dose group or 3 tablets of 14.5 mg SENS-401, twice daily (morning and evening), oral route. Depending upon the final dose selected, if this dose is the non-selected dose, it will be stopped immediately after the decision is taken
- Placebo group: 3 matching placebo tablets twice daily (morning and evening), oral route

Duration: Given for 28 days.

Administration Route: The tablets must be swallowed with water

## 9.2 Non-Investigational Product

There is no medical treatment recommended by the medical societies. However, all patients will receive concomitantly oral corticosteroids, unless contra-indicated, which is standard of care treatment. The type and dose will be at the discretion of the investigator and recorded in the e-CRF. Administration of intratympanic treatments, including corticosteroids, is not authorized until day 14. A rescue treatment with intratympanic corticosteroids may be proposed from day 14 in case of non-response.

## 9.3 Description of blinding methods

The SENS-401 and placebo tablet are identical.

Two lists of randomisation using a 1:1:1 randomisation ratio will be generated for the whole study, one for the French sites involved in the ancillary study and one for all the other sites globally, including French sites not participating in the ancillary study.

During Part 1, the 3 treatment arms will be used. During Part 2 the 3 treatment arms will continue to be allocated until one active dose is selected. After dose selection, only the placebo and the selected active dose will continue to be allocated.

The lists of randomisation will be generated centrally, and the investigator, the sponsor study team, the CRO or subjects will be blinded to the Investigational drug administration. The lists of randomisation will be stratified by the duration of the disease at baseline (≥24 hours or < 24 hours) and oral corticosteroids intake at baseline (no, yes).

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 randomisation code except under special circumstances. In case of an emergency, when knowledge of the randomisation status is deemed necessary for the medical care of the patient, the randomisation code can be unblinded for a specific patient (see section 11.3.4).

### 9.4 Randomisation process

The randomisation will be managed centrally using an interactive web response system (IWRS). The IWRS allocates a treatment number to the patient according to the relevant randomisation list (non ancillary study sites or ancillary study sites), and the further stratification on the duration of the disease (≥24 hours or < 24 hours), and oral corticosteroids intake at baseline (no, yes). During the course of the study, one of the two active treatment arms may be disabled (dose dropped after decision of Part 2).

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

All randomised subjects (Day 1) will receive either SENS 29 mg, or SENS 43.5 mg or Placebo treatment at the study site according to the IWRS allocation.
The treatment will be then self-administered twice daily to all patients for 28 days.
A patient cannot be randomised more than once during the study.

### 9.5 Packaging and labeling

SENS-401 and matching placebo will be inserted in bottles with a child resistant cap. The bottles are packaged and labeled into a sealed clinical pack that includes 3 bottles including 30 tablets each of the investigational product or placebo for a 14-day administration including 1 additional day (rescue tablets). Twice daily, each patient will take 3 tablets (one tablet from each of the 3 bottles) included in one assigned pack. Each patient will receive 2 clinical packs (inserted into a final pack) according to the randomisation lists. During the 28-day treatment period, in exceptional case of any bottle being lost, the IWRS can allocate a replacement treatment number to a patient. The first dose to be administered at the study site will be taken out from one of the clinical packs that will be dispensed to the patient on Day 1 (visit 2), to be taken home. The content of the labeling is in accordance with the local regulatory specifications and requirements.

## 9.6 Accountability and compliance

The date and time of the first intake will be recorded on the eCRF.
The patient will be instructed to return all used and unused investigational kits at every on-site visit. He/she will be provided a diary to record the intake of IP (number of tablets, date and time). The investigator or designee will count the returned tablets and complete the corresponding e-CRF.

The type and dose of corticosteroids will be recorded on the eCRF. The patient will record the intake of corticosteroid in the diary. Corticosteroids intake will be also recorded on the e-CRF, based on the patient's information.

## 9.7 Storage conditions

SENS-401 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 regulation, and label specifications.
Patients should be warned to store the treatment according to the labeling and out of reach of children. They will be warned not to take the tablets out of the bottles in advance. They will be requested to return the bottles with the remaining tablets at the following on site visit.

## 9.8 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.

## 9.9 Management of treatment at the end of the study

All partially used or unused investigational product (IP) will be returned to Sensorion or designee 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.

## 9.10 Concomitant treatment

### 9.10.1 Background therapy

Corticosteroids by oral route (including but not limited to prednisone, methyl prednisolone, dexamethasone) are usually considered as the standard of care (Appendix 6). The guidelines published by the AAO-HNS recommend prednisone for patients with SSNHL within 2 weeks after the diagnosis, with a recommended dose of Prednisone 1 mg/kg/day (max: 60 mg/day), or Methylprednisolone 48 mg/d or Dexamethasone 10 mg/d given as a single dose for 7-14 days, then taper over similar time period. Since there is no harmonization on this clinical practice,

each site will be requested to pre-specify the type and dosage regimen of oral corticosteroid that will be given to patients as standard of care. Unless contra-indicated, the pre-specified oral corticosteroids will be prescribed to all patients at a given site. The time, dose and route of administration will be recorded on the e-CRF. The randomisation will be stratified according to the corticosteroid intake. Compliance of the corticosteroids intake will be assessed by the investigator at every on-site visit from the patient diary. Any contra-indication will be recorded on the e-CRF at the sites.

### 9.10.2 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 new 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 on the e-CRF.

### 9.10.3 Not permitted concomitant medication

The medications listed below are not permitted, unless in exceptional circumstances (see below rescue medication):
Corticosteroids by intratympanic route (including but not limited to prednisone, methyl prednisolone, dexamethasone) is not permitted except from D14 where they can be given as rescue medication (see criteria in section 9.9.3.)

Other intratympanic treatments

Hyperbaric oxygen

Antivirals, vasodilators, vasoactive substances, or antioxidants. In case of chronic treatment for reasons other than inner ear diseases, these agents can be continued but the dose regimen must not be modified until the end of the treatment period

Any investigational drug,

Any ototoxic treatment (e.g. aminoglycosides, cisplatin, loop diuretics, quinine etc.)

Initiation of antidepressant treatment containing serotoninergic agents within the previous 24 hours (see non-exhaustive list of serotoninergic agents in Appendix 7) due to the risk of serotoninergic syndrome.

Substrates of BCRP and transporter (see non-exhaustive list in Appendix 8)

5 $HT_3$ antagonists (ondansetron, tropisetron, palonosetron, granisetron etc..) and calcineurin inhibitors (cyclosporine, tacrolimus, azasetron)

Any additional medication aiming at treating SSNHL must be discussed with the monitoring team.

### 9.10.4 Rescue medication

Despite the absence of evidence, the American Academy of Otolaryngology- Head and neck surgery (AAO-HNS) recommends the use of rescue treatment to patients without hearing improvement. Hearing is considered improved if the change in hearing loss is 10 dB or more in the 3 contiguous frequencies compared to the worst hearing threshold of the affected ear as identified at study entry. Rescue medication consists of intratympanic administration of corticosteroids (Appendix 6). The type of drug and number of injections are not specified. Rescue medication may be proposed from-Day 14 only in patients without hearing

improvement as defined above. The rescue medication (date, dose, indication) should be recorded on the e-CRF.

# 10 STUDY ASSESSMENTS

Test equipment, test environment, and test procedures must meet all relevant national standards and guidelines. All audiologic testings should be conducted in a quiet testing environment meeting appropriate current standards. The patients should be seated in a comfortable position. Before each audiologic evaluation, a quiet period or lack of noise for 16 to 24 hours is required. **For a given patient, the same** certified and trained **audiologist will perform the tests.** Any exception should be justified.

## 10.1 Efficacy assessments

### 10.1.1 Pure Tone Audiometry

Pure tone audiometry is considered the diagnostic gold standard for assessing SSNHL (11) (24). The primary purpose of pure tone audiometry is to determine the degree, type and configuration of hearing loss as its measurement covers the entire auditory pathway from the external ear to the cortex.

It is a standardized subjective hearing test in which air and bone-conduction hearing thresholds in decibels (dB) for a set of fixed frequencies between 0.25 kHz and 8 kHz are plotted on an audiogram for each ear independently.

Audiometry will be performed in order to determine the pure-tone air-conduction and bone-conduction thresholds for each ear according to the recommended procedure of the British Society of Audiology and the guidelines of the American Speech Language Hearing Association (ASHA).

The detailed procedures will be described in a specific manual. All materials will need to be calibrated before the study start and on a monthly basis, following ASHA, American Association of Autology (AAA), American National Standards Institute (ANSI) recommendations and military standards where applicable (6), (7), (8), (9).

At the inclusion visit, pure-tone air-conduction testing should be immediately repeated at 1 and 2 kHz to determine that the subject provides reliable responses. Responses are considered reliable if retest thresholds at both frequencies do not exceed ±5dB of the previously obtained threshold response.

Pure tone air and bone conduction thresholds will be determined for each ear (best ear at first) at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz for air conduction and 0.5, 1, 2, 3, 4 kHz for bone conduction using the descending method of limits (modified Hughson Westlake procedure as follows: initial descent towards threshold is accomplished in 10-dB steps. Beginning with the first non-response, level is increased by 5-dB for each non- response and decreased by 10-dB after each correct detection response.

The baseline pure tone audiometry test is the last test performed at site within 24 hours prior to the first study drug administration. In case of longer time or if a pure tone audiometry test was performed elsewhere than at study site, the test should be repeated prior to the first study drug intake. If a screening test has been performed at the study site within 24 hours prior to the first study drug intake, there is no need to repeat it.

**The hearing threshold** is defined as the lowest audible level, measured twice out of three presentations for that patient. The thresholds at each frequency for each ear for both air and bone pure tone audiometry will be recorded on the e-CRF at each study visit. The information will be captured in case of no response because of profound hearing loss.

The **hearing loss** will be determined as follows: Difference between the mean hearing threshold at the 3 most affected contiguous test frequencies (air pure tone average) and the corresponding mean hearing threshold of the contralateral ear or values from a pre-existing audiogram (dated less than 2 years) for the same frequencies (mandatory for bilateral acute acoustic trauma).
The Pure tone average frequencies determined at baseline will remain fixed for all evaluations.
In case of bilateral acute acoustic trauma leading to sudden sensorineural hearing loss, the most affected ear according to the inclusion criteria will be considered for the analysis. If both ears are equally affected, the right ear will be considered.
In case of one missing frequency in any of the post baseline measurement, the PTA will be determined on the 2 out of the 3 available frequencies. An absolute improvement of 10dB is considered clinically meaningful.

### 10.1.2 Speech audiometry

Speech audiometry is a diagnostic hearing test designed to test word or speech recognition. It has become a fundamental tool in hearing-loss assessment. In conjunction with pure-tone audiometry, it can aid in determining the degree and type of hearing loss. Speech audiometry also provides information regarding discomfort or tolerance to speech stimuli and information on word recognition abilities.
Speech audiometry will be performed according to the guidelines of the American Speech Language Hearing Association (10).

**The Speech recognition threshold** is the minimum hearing level at which the patient can correctly recognizes the speech stimuli 50 % of the presented speech material. Spondaic words are the usual and recommended test material for the speech recognition threshold; spondaic words are two-syllable words with equal stress on both syllables (e.g. birthday)
According to the ASHA guidelines, patients will be familiarized with the spondaic words prior to the test. Patients will listen to the list of words and indicate if any are unfamiliar. These words can be eliminated from the list. The median speech reception threshold (SRT) for normal listeners is 20 dB SPL (0 dB HL).
The standard amount of time given for the patient to respond is approximately four seconds.
The list of spondees adapted to local languages will be standardized across all centers in a given country.
The speech recognition threshold will be recorded on the e-CRF.

**The speech discrimination or word recognition** is the ability to repeat correctly an open set of monosyllabic words at supra threshold intensity. **The word recognition score (WRS)** is the percentage of test words correctly repeated by the patient.
The test will be administered in a quiet room without any competing noise. Word lists are derived from a standard list with language-specific monosyllabic words.
Words are presented randomly to each ear separately, with contralateral masking. They are phonetically balanced, meaning that the speech sounds used occur with the same frequency as in the whole language. In order to alert the patient, patients will be instructed to repeat the word, as follows: ***"(Say the word …)".***
At the inclusion visit (day 1) visit 2, words will be presented at 60dB and 80dB. The WRS (percent correct rate) will be further derived by computerization.

An absolute improvement of ≥15% is considered clinically meaningful.

### 10.1.3 Tinnitus

Tinnitus is often associated with SSNHL. It is defined as the hearing of sound when no external sound is present. While often described as a ringing, it may also sound like a clicking, hiss or roaring.
If the patient presents tinnitus in both ears, only the severity of the tinnitus in the ear affected by SSNHL will be assessed on a numerical scale (NRS). For the Tinnitus NRS, the patients will be asked to rate tinnitus loudness ‘‘right now’’ on a scale scored from 0 (no tinnitus) to 10 (extremely loud). The Tinnitus NRS score will be recorded on the e-CRF at each study visit.

In addition, the patients will be given a diary for recording the presence and the severity of the tinnitus (if any) on a daily basis during the first 14 days of treatment.

### 10.1.4 Vertigo

The presence and severity (if relevant) of the vertigo will be assessed on a numerical scale. For the vertigo NRS, the patients reporting vertigo will be asked to assess if present and rate its severity ‘‘right now’’at V2, then in the past week from V3 on a scale scored from 0 (no vertigo) to 10 (extreme vertigo). The vertigo NRS score will be recorded on the e-CRF at each study visit.

### 10.1.5 QoL

1) EQ-5D-5L
Hearing loss with tinnitus can affect the patient quality of life which can be assessed by various tools including EuroQoL (28).

EQ-5D is a standardized measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. EuroQoL, consists of two parts: the health-status descriptive system (EuroQoL 5-dimension, EQ-5D) and the EQ visual analogue scale.

The EQ-5D-5L version records the level of self-reported problems according to five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

Each dimension is assessed based on a single question with five response levels (no problem, slight problems, moderate problems, severe problems and extreme problems), to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient’s health state.

The EQ VAS records the patient’s self-rated health on a vertical visual analogue scale ranging 0 to 100, where the endpoints are labelled “The best health you can imagine” (100) and “The worst health you can imagine” (0). The VAS can be used as a quantitative measure of health outcome that reflect the patient’s own judgement.

The EQ-5D-5L will be completed at every visit from visit 2. Results will be recorded on the e-CRF (see appendix 2).

**2) The tinnitus functional index (TFI)**

The impact of tinnitus on quality of life will be also assessed through a specific scale, the Tinnitus functional Index (TFI) (26) (see Appendix17).

The TFI comprises 25 questions on the impact of the tinnitus on the individual behavior and feelings. It includes eight subscales that address the intrusiveness of tinnitus, the sense of control the patient has, cognitive interference, sleep disturbance, auditory issues, relaxation issues, quality of life, and emotional distress.
The TFI will be completed at every visit from visit 2. Results will be recorded on the e-CRF

### 10.1.6 Otoacoustic emissions (optional)

Otoacoustic emissions (OAEs) are low-intensity sounds generated by the inner ear when the cochlea is stimulated by a sound (functioning outer hair cells of the cochlea). When sound stimulates the cochlea, the outer hair cells vibrate. The vibration produces a nearly inaudible sound that echoes back into the middle ear. The sound can be measured with a small probe inserted into the ear canal.
OAEs recording is an objective neurophysiological test reflecting the function of the inner ear outer hair cells (OHCs) (29).
People with normal hearing produce emissions. Those with hearing loss greater than 25–30 decibels (dB) do not produce these very soft sounds.
The evoked OAEs include the transient evoked otoacoustic emissions (TEOAEs) and the distortion products otoacoustic emissions (DPOAEs). TEOAEs and DPOAEs are either present (recordable) or absent (non-recordable) in physiological conditions.
Some authors suggested a potential role of TEOAEs and DPOAEs early evaluation in the prediction of the ISSNHL prognosis (48). The early detectability of TEAOAEs and DPOAEs preceding pure tone audiometry hearing improvement might be explained by the high sensitivity of those testing modalities of changing the outer hair cells activity.

OAEs are measured by acoustic stimuli such as a series of very brief clicks to the ear through a probe that is inserted in the outer third of the ear canal. The probe contains loudspeakers that generate the clicks and a microphone for measuring the resulting OAEs. OAE testing requires no behavioral or interactive feedback by the individual being tested.

Two pure tones (f1, f2) are simultaneously presented at 2 separate frequencies. DPOAEs originate from the cochlea when the two tones are closely related frequencies that activate the cochlea at a specific region of the basilar membrane corresponding to the f2 frequency. The DPOAEs are thought to reflect the outer hair cells activity at the supra-threshold level (31).
For the TEOAE, a single brief click that covers a broad frequency range activates wide regions of the basilar membrane and reflects the OHCs activity at the threshold level (cochlear function).

Thus, although both evoked OAEs measure the OHCs function, they reflect different ranges of their activity. Presence or Absence of TEOAEs and DPOAEs will be recorded on the e-CRF at each study visit, at sites conducting these tests.
For each tested frequency, the results of the 2f1-f2 level and of the Signal-to-noise ratio S/N (in dB SPL) will be recorded in the e-CRF for DPOAE.
For each tested frequency, the results of the Echo SPL level and of the Signal-to-noise ratio S/N (in dB SPL) as well as the Whole Wave reproducibility (WWR) (%) of the test for each ear will be recorded in the e-CRF for TEOAE.

## 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 height, weight, Body Mass Index (BMI) and evaluation of main body systems/regions, including: skin and mucous, eyes/nose/throat, pulmonary, cardiac, gastro-intestinal and neurological systems is to be conducted at the screening visit (Visit 1), End of treatment (Visit 5) and End of Study (Visit 6).
A specific attention will be paid to neurological, head and neck, as well as otologic systems. Care should be taken to examine and assess any abnormalities that have been indicated as potentially present by medical history.

### 10.2.2 Otologic and audiologic examination

Otoscopy is to be done just before each hearing assessment at every visit to rule out possible outer-ear abnormality, such as otitis media, tympanic perforation. It is part of the standard of care. Tympanometry will follow the otoscopy in order to test the condition of the middle ear and mobility of the eardrum (tympanic membrane) and the conduction bones by creating variations of air pressure in the ear canal. There is no need to repeat the tests if it has been conducted within 6 hours prior to the screening visit.

### 10.2.3 Vital signs

Vital signs including temperature, systolic (SBP) and diastolic (DBP) blood pressures, heart rate will be collected after 10 minutes rest in the supine position.
Vital signs will be measured at each study visit, if possible, prior to blood draw (when relevant).

### 10.2.4 Electrocardiogram (ECG)

A standard digitalized 12-lead electrocardiogram (ECG) will be performed at baseline (Visit 2) prior to randomisation, on Day 7 (Visit 3), Day 14 (Visit 4), and End of treatment visit Day 28 (Visit 5). Each ECG will be triplicated. Ideally at V4 and V5 least one of the PK samples MUST be collected within 15 minutes of the 3rd ECG test being performed.

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 digitalized ECG, collected in triplicate, will be managed with a central reading. Corrections of the QT interval will be calculated using Fridericia's and Bazett's formula. Changes from the baseline QT interval will also be assessed.

### 10.2.5 Laboratory safety

A standard laboratory blood test will be performed at the screening visit (Visit1), on Day 14 (Visit 4), and End of treatment visit Day 28 (Visit 5) also performed in case of Early termination between Visit 2 and Visit 5. Routine serum hematology and chemistry samples will be collected in EDTA tubes and according to the study flow chart. They will be kept at the local

laboratory as per laboratory requirements and outlined in the investigator manual which will be available at each investigational site.

The standard laboratory blood test comprises:

- haematology: complete blood count (CBC) including haematocrit, haemoglobin, red blood cell count, white blood cell count with differential count and platelets,
- Serum chemistry including: sodium, potassium, chloride, calcium, phosphorous, urea, creatinine, creatinine clearance (calculated with the Cockroft-Gault formula for patients <65 years old and CKD-EPI creatinine equation or with MDRD equation for patients ≥65 years old), uric acid, total protein, albumin, lactate dehydrogenase (LDH), Alanine Aminotransferase (ALT), Aspartate Transaminase (ASAT), alkaline phosphatase, GGT and total bilirubin, fasting glycaemia (fasting is not required at baseline), creatine phosphokinase (CPK), triglycerides, cholesterol.
- Glucose (no fasting is needed at screening)
- C Reactive Protein (CRP).
- A urine or blood pregnancy test (in females of childbearing potential) will be performed at the screening visit, on D14 (Visit 4), end of treatment visit (D28 visit 5) and end of study visit (D 84 Visit 6). 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. For practicability, urine samples may be replaced by blood samples.

No centralized laboratory procedure for laboratory safety is planned. Only local laboratories will be used.

### 10.2.6 Adverse event collection

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

As a precautionary measure, specific attention will be paid to any potential serotoninergic syndrome, particularly the following symptoms agitation, mental status changes (confusion, hypomania), myoclonus, shivering, tremor, hyperreflexia, ataxia, severe diarrhea or high fever will be checked carefully.

### 10.2.7 Suicidality assessment:

As per FDA guidelines for any neurologic investigational product, a suicidality assessment will be performed via the C-SSRS questionnaires (42) that will be completed at every visit from visit 2 until end of treatment visit (visit 5) by a trained personal. A series of questions about suicidal thoughts and behaviors will be asked. To most quickly and simply identify whether a person is at risk and needs assistance, a minimum of two and a maximum of six questions, depending on the answers will be asked. The patient should answer yes or no to the questions.

The C-SSRS questions use plain and direct language, which is most effective in eliciting honest and clear responses. This scale has been widely used in clinical trials and is translated in many languages. It has been validated by most of health authorities.

Results could trigger decisions about hospitalisation, counseling, referrals, and other actions. If any, an adverse event form should be completed.

### 10.3 Pharmacokinetic evaluation

Serum samples will be collected for pharmacokinetic (PK) analysis on Day 14 (Visit 4) and End of treatment visit (Visit 5): for more details, please refer to the laboratory manual. Ideally at least one V4 and V5 PK samples MUST be collected within 15 minutes of the 3rd ECG test being performed. Blood samples will be drawn, handled and stored in a secure location as per laboratory requirements, outlined in the laboratory manual which will be available at each investigational site, until shipment. The date and hour of the last drug intake and blood sampling will be recorded.

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 Biomarker

Prestin has been described as a potential prognosis biomarker (40). Serum samples will be collected for prestin dosage at inclusion (Visit 2), or screening (Visit 1) in case the screening and inclusion visits are planned to be performed within 24hrs (to prevent an additional blood draw for a small blood volume), on Day 14 (Visit 4), and End of treatment visit (Visit 5). Blood samples will be drawn, handled and stored in a secure location as per laboratory requirements, outlined in the laboratory manual which will be available at each investigational site, until shipment. The date and hour of the last drug intake and blood sampling will be recorded.

# 11 STUDY PROCEDURES

## 11.1 Visits

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 the follow-up visits during the defined window periods.

A final follow-up visit is required for all patients. In the rare cases the End of Study Visit (V6) cannot occur, any attempt to contact the patient should be recorded on a special contact form, until/unless appropriate information is obtained which will allow completion of final follow-up visit in the e-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 concerned patient.

Patients will be advised to avoid skin exposure to strong sunlight and to wear sunglasses in bright sunlight for the duration of the study and for 1 week after the last dose.

### 11.1.1 Screening visit - Visit 1 (Day-4 to Day 1)

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 the investigator or a fully designated person, 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 e-CRF Portal, site 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, including body weight and evaluation of main body systems/regions,
- Otologic examination and tympanometry
- Pure tone audiometry test unless performed within 24 hours prior to screening.
- Previous Medical, surgical and otologic history
- Concomitant medications (over the past 3 months)
- Recording of concomitant medication including oral corticosteroid use for SSNHL

- Vital signs: supine blood pressure and heart rate, temperature
- Blood collection for routine hematology, serum chemistry (section 9.2.4)
- Pregnancy test (for WOCBP)

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

### 11.1.2 Baseline visit - Visit 2 (Day 1)

The following tests and procedures will be performed:

- Re-confirmation of eligibility by reviewing inclusion/exclusion criteria
- Checking for Concomitant medication
- Inquiring about adverse event and fill an adverse event form if any
- Recording of concomitant medication including oral corticosteroid use for SSNHL
- Vital signs: blood pressure and heart rate, temperature
- 12-lead digitalised ECG
- Otologic examination and tympanometry*
- Audiometric tests: pure tone audiometry*, OAE tests (optional)
- Word and speech recognition Tests
- Serum sample for Prestin concentration (before study drug intake)

The patient will be asked to complete specific questionnaires:

- Tinnitus and Vertigo presence and severity (NRS)
- QoL: EQ-5D-5L;
- TFI
- C-SSRS

*Pure tone audiometry should be performed within the last 24 hours before the first study drug intake. In case of longer time or not performed at the study site, the Pure tone audiometry should be repeated. If a Pure tone audiometry was performed at the study site for screening less than 24 hours before the first study drug intake, there is no need to repeat it.

After all assessments have been completed, the investigator will connect to the IWRS for allocation of a randomised 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 3 tablets (one from each bottle of one clinical pack). Date and time of the intake should be recorded on the patient diary and e-CRF.

The patient will be given the treatment carton to be taken home and asked to complete a patient diary for IP and corticosteroid compliance. The patient will be instructed to return his/her treatment carton and diary at the following visit.

The patient will also be asked to record tinnitus presence and intensity in the SSNHL affected ear on a daily basis in the patient diary. He will be asked to return the diary at the following visit.

#### 11.1.3 Visit 3 (Day 7 ±2)

The following tests and procedures will be performed:

- Checking for concomitant medication
- Inquiring about adverse event and fill an adverse event form if any
- Checking the patient's diary for tinnitus
- The investigator or designee will check the IP and oral corticosteroids diary for compliance.
- Vital signs: blood pressure and heart rate, temperature
- 12-lead digitalized ECG
- Otologic examination and tympanometry
- Audiometric tests: Pure tone audiometry, OAE tests (optional)
- Word and speech recognition Tests

The patient will be asked to complete specific questionnaires:

- Tinnitus and Vertigo presence and Severity (NRS)
- QoL: EQ-5D-5L;
- Tinnitus functional Index (TFI)
- C-SSRS

The patient will be asked to complete a new patient diary for IP and corticosteroid compliance. The patient will be instructed to return his/her treatment carton and diary at the following visit. The patient will be given back the treatment carton to be taken home. The patient will be reminded to record tinnitus presence and intensity in the SSNHL affected ear on a daily basis, and IP and corticosteroid intake. He will be asked to return the diary at the following visit, and to come in a fasting condition and not take the morning IP dose whenever the visit 4 is scheduled in the morning to allow a Pre-dose PK at Visit 4.

#### 11.1.4 Visit 4 (Day 14 ±2)

The following tests and procedures will be performed:

- Checking for concomitant medication
- Inquiring about adverse event and fill an adverse event form if any
- The investigator or designee will check the IP and oral corticosteroids diary for compliance
- Checking the patient's diary for tinnitus
- Otologic examination and tympanometry

- Vital signs: blood pressure and heart rate, temperature
- 12-lead digitalised ECG
- Blood collection for routine hematology and serum chemistry (section 9.2.4)
- Serum sample for prestin and plasma sample for drug concentrations
- Audiometric tests: Pure tone audiometry and OAE tests (optional)
- Word and speech recognition Tests
- Pregnancy test (for WOCBP)

In case rescue medication is administered, please report in the e-CRF

The patient will be asked to complete specific questionnaires:

- Tinnitus and Vertigo Presence and Severity (NRS)
- QoL: EQ-5D-5L;
- TFI
- C-SSRS

The patient will be asked to complete a new patient diary for IP and corticosteroid compliance. The patient will be instructed to return his/her treatment carton and diary at the following visit,

The patient will be instructed to return all used and unused study treatment bottles at the following visit and to come in a fasting condition.

#### 11.1.5 Visit 5: End of Treatment Visit (Day 28±3)

The following tests and procedures will be performed:

- Checking for concomitant medication
- Inquiring about adverse event and fill an adverse event form if any
- The investigator or designee will count the returned IP tablets
- The investigator or designee will check the oral corticosteroids diary
- Otologic examination and tympanometry
- Complete Physical examination including weight and evaluation of main body systems/regions,
- Vital signs: Blood pressure and heart rate, temperature
- 12-lead digitalized ECG
- Audiometric tests: Pure tone audiometry and OAE tests (optional)
- Word and Speech Recognition Tests
- Blood collection for routine hematology and serum chemistry (section 9.2.4)
- Serum sample for prestin and plasma sample for drug concentrations
- Pregnancy test (for WOCBP)

In case rescue medication has been administered, please report in the e-CRF.

The patient will be asked to complete specific questionnaires:

- Tinnitus and Vertigo Severity (NRS)
- QoL: EQ-5D-5L
- TFI
- C-SSRS

#### 11.1.6 Visit 6 End Study visit (Day 84±3)

The following tests and procedures will be performed at Visit 6 and in the case of premature withdrawal during the study (i.e. prior to Visit 6):

- Inquiring about adverse event and fill an adverse event form if any
- Checking for concomitant medication
- Physical examination including weight and evaluation of main body systems/regions,
- Vital signs: supine blood pressure and heart rate, temperature
- Otologic examination and tympanometry
- Audiometric tests: Pure tone audiometry and OAE tests (optional)
- Word and Speech recognition Tests
- Pregnancy test (for WOCBP)

The patient will be asked to complete specific questionnaires:

- Tinnitus and Vertigo Severity (NRS)
- QoL: EQ-5D-5L
- TFI

#### 11.1.7 Unscheduled Visit: Visit 99

In case of adverse event, abnormal values or dispensation of a replacement IMP kit, an additional visit may be needed to repeat the test or document an adverse event or to dispense a new IMP kit.

### 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 Appendix 5.

The results of certain investigations or assessments included on the e-CRF may be considered to be raw data. Direct e-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 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 (V6) if discontinuation occurs after Visit 5 or the end of Treatment Visit (V5) if discontinuation occurs before Visit 5.

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

- Any serious or severe (CTCAE GRADE 3) related adverse event will lead to permanent treatment discontinuation
- Adverse events of lesser grade should be evaluated in the context of concomitant clinical and laboratory findings and, in the judgment of the Investigator and responsible medical officers, may be cause for temporary or permanent discontinuation of treatment for an individual subject. If interruption of treatment for an individual subject is required due to adverse events more than once during the trial, then the subject will be withdrawn from further treatment.
- Significant laboratory abnormalities
  - Confirmed ALT > 5 ULN (or > 3 times baseline value if ALT > ULN at baseline) or in case of confirmed ALT >3 ULN and total bilirubin >2 ULN (unless the patient has Gilbert's disease documented by genetic testing)
  - Confirmed, non-rapidly reversible, increase in serum creatinine ≥ 1.7 mg/dL (150 µmol/L) or rapid decrease in creatinine clearance reaching < 50 ml/min-
  - Confirmed rhabdomyolysis (CPK should be controlled in case of suspicion)
  - Confirmed decline in hemoglobin of > 3 g/dL compared to baseline and hemoglobin

level grade 1 (< LLN - 10 g/dL) or higher of CTCAE terminology

- Confirmed platelet count < 100,000 cells/$mm^3$ with or without spontaneous bleeding
- Confirmed decline in total white blood cell count of > 50% compared to baseline and white blood cell count grade 1 or higher of CTCAE terminology (< LLN - 3000/$mm^3$)
- Confirmed neutrophil count < 1500/$mm^3$ with or without signs of infection
- Confirmed decline in lymphocyte count of > 50% compared to baseline and lymphocyte count grade 2 (< LLN - 500/$mm^3$) or higher of CTCAE terminology
- Confirmed elevated INR grade 3 (> 2.5 x ULN) or higher of CTCAE terminology
- Confirmed QTc > 500 ms

Note: Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of IMP for the concerned patient.

- Any adverse events, per investigator judgment, that may jeopardize the patient safety
- Any patient with a temporary discontinuation for safety reasons that is greater than or equal to 10 consecutive days from last IMP administration
- Any treatment unblinded by the Investigator
- Noncompliance with study protocol by the subject.

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 e-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 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 (IP) that could change the current benefit-risk profile of the IP or that would be sufficient to require changes in the IP administration or in the overall conduct of the trial.
- The total number of subjects included earlier than expected.

- Discontinuation recommended by the DMC after a GST interim look in case of futility or because of efficacy of the highest tested dose (see Statistical considerations)
- Unexpected events that could jeopardize the conduct and quality of the study. These events could be any of the followings: Conflicts in a specific country, Major climatic reasons or earthquakes, Unexpected epidemics (eg. SRAS), Financial issues (funding does not match the incurring costs), External constraints that could prevent IP distribution etc.…External events not yet identified.

In any case, the exact reason of termination will be specified and the ethics committee informed within 15 days after the decision is taken.

### 11.3.4 Decided by the investigator

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

In all cases IEC/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 unfavourable 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.

**Lack of efficacy unless considered serious, should not be reported as adverse event. The Pure tone audiometry assessment is part of the efficacy assessment, as well as the administration of rescue treatment.**

### 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 hospitalisation or prolongation of existing hospitalisation. Prolongation of existing hospitalisation 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 hospitalisation, 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 hospitalisation; 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.

## 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-401, 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 Pregnancy

If a female participating in the study becomes pregnant during the study (positive pregnancy test after 1 dose), the investigator must stop the treatment and notify it as a Serious Adverse event.

The occurrence of a pregnancy of a partner of a trial subject discovered during the study (start pregnancy after 1st dose) or within 10 days after last administration of the IP 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.

In all cases, the investigator will contribute to the pregnancy follow-up.

## 12.4 Reporting of adverse events

### 12.4.1 Adverse events

Any AE occurring after the patient has signed the informed consent must be fully recorded on the patient's e-CRF. The AE form should be supported by a complete documentation available in the patient's file.

Any abnormal laboratory test or ECG 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 test should be repeated as soon as possible for confirmation. The AE should be fully described along with start and stop dates, severity, relations 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 treatment 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).

### 12.4.2 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.

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/IRB in writing in accordance with current regulations.

### 12.4.3 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:

- Unrelated: 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.
- 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 effect. 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.

## 12.5 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 medical monitor by phone or email and the monitoring team using the specific e-CRF form. The sponsor or designee will inform the authorities.

## 12.6 Safety follow-up

- The Investigator should take all appropriate measures to ensure the safety of the subjects. All patients 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 (V6).
- 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.

## 12.7 Unblinding procedure

In case of an emergency, the Investigator can unblind the treatment for a specific patient through IWRS that will be available 24h/24h and 7days a week.

Unblinded subjects must be discontinued from the study.

## 12.8 General Safety Monitoring

### 12.8.1 Data Monitoring Committee

An external data monitoring committee (DMC), consisting of two or more physicians and a statistician, 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, as well as the efficacy when the last (Day 28) visit of Part 1 is reached or if an interim GST look recommends premature discontinuation of Part 1.

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 first review is expected to be done after 30 patients have completed the study.

The DMC will meet regularly to review the blinded safety information as follows:

- The number of screened and included patients and demography (gender, age)
- The total number of AEs and SAE per treatment groups, displayed by preferred term.
- The ECG database provided by central reader
- The clinically significant abnormal laboratory values

In addition, the DMC members will receive the EDC SAE alerts by email that are automatically triggered when a site enters a SAE in the eCRF. The PV representative will provide each SAE blinded report for this study to the DMC members for their consideration within 7 days in case of fatal or life threatening events or within 15 days in case of other SAEs from the time Drug Safety has received the report.

In case of SUSAR or any other relevant SAE, the DMC will re-evaluate the risk for the patients to allow or not the continuation of the study.

The final list of adverse events to be reviewed will be discussed and finalized by the DMC members during the kick off meeting prior to the start of the study and appended to the signed DMC charter. It will be sent upon request to European or National authorities.During Part 1, two interim efficacy looks are planned. They will be performed by an independent statistician dedicated to the Group Sequential Test (GST) (see section about Possible changes during Part 1). Each of these interim looks will lead to an automatically generated recommendation to the sponsor of continuing the study for efficacy or futility respectively.

The committee will review the results and will provide further recommendation to the sponsor for stopping Part 1for efficacy or futility or continuing the study as planned, until the next look or the final analysis of Part 1.

No information about these results will be communicated to investigators and the International Coordinating Investigator until the study is completed or discontinued.

The committee will be responsible for selecting the active dose to be tested in Part 2. The committee will be provided with the unblinded efficacy data on the primary end-point when 111 patients randomised to Part 1 have completed the 4-week treatment. The DMC may also recommend to modify the sample size of the Part 2 study.

# 13 STATISTICAL CONSIDERATIONS

The two parts of the study (Part 1 and Part 2) will be analysed separately.

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.
All statistical analyses will be displayed on total population and on the 2 subgroups: non-ancillary studiy sites and ancillary study sites.
SAS Version 9.4 or later will be used for statistical programming.

## 13.1 Determination of sample size

The sample size is based on the primary end-point: average change in air conduction derived from PTA in dB between the baseline and week 4 (Day 28±3d) on the 3 most affected contiguous frequencies.

Part 1: A sample size of 111 patients (37 patients per treatment arm) was retained corresponding to following assumptions:

- Each comparison to placebo performed at 5% one-sided significance level (with higher dose to be tested first and low dose to be tested conditionally to the high dose significance).
- Power of each comparison to placebo set to 7575%.
- Randomisation ratio 1:1:1.
- Intra-group standard deviation of 30 dB is estimated based on recent publication in SSNHL with other pharmaceutical therapies and blinded examination of variance (a 0.45 correlation between Day 28 and baseline).
- A difference to placebo of 15 dB is expected, which would be considered clinically meaningful.
- The corresponding fixed design sample size of 105 patients (35 patients per treatment arm) was then inflated to 111 patients (37 patients per treatment arm) to allow the use of a GST design with 3 looks (2 interim looks and a final look).

This design of Part 1 was introduced in the protocol amendment leading to version 4.0. The revised assumption of the intra-group standard deviation (adjusted for baseline) of 30 dB was based on a blinded review of the variability of 63 patients, which led to an estimate of the adjusted standard deviation more in line with the 27 dB seen in a recent publication in SSNHL (52) than with the 20dB seen in the publication used at time of the protocol initiation (53). The choice of the power level and of the significance level, combined with the strategy of testing the low dose conditionally after the high dose, was guided by the unexpected low recruitment rate observed in the study. The 3-look GST design (interim looks plus one final part 1 analysis) was introduced in order to allow an early discontinuation (for futility or for efficacy) of Part 1. The first GST look was performed and the outcome was a recommendation to continue Part 1 in the absence of crossing of any boundary.

Part 2: A sample size of 190 patients (95 patients per treatment arm) was retained corresponding to following assumptions:

- Comparison to placebo performed at 5% two-sided significance level
- Power of the comparison to placebo set to 90%.
- Randomisation ratio 1:1
- Intra-group standard deviation of 20 dB is estimated based on recent publication in SSNHL with other pharmaceutical therapies.
- A difference to placebo of 10 dB is expected as considered clinically meaningful
- 10% dropout rate

The sample size of Part 2 will be re-estimated based on Part1 results when available.
The final sample size will be submitted for approval to competent authorities prior to the pivotal part start

## 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 (those who have signed an informed consent),
- Included subjects (= randomised: those who receive a treatment number),
- Exposed subjects (those who take at least one dose of randomised study drug),
- Completed subjects,
- Reasons for treatment discontinuation

In summary tables, a breakdown by center and randomised 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 randomised 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 randomised 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 randomised subjects as denominator.

### 13.2.2 Protocol deviations

Protocol deviations will be identified and classified. These deviations will be described in the statistical analysis plan. 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 randomised patients according to randomisation 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 Handling of missing data:

The primary end-point is the absolute change in PTA (in dB) from baseline to the end of treatment visit (D28) based on the average on the 3 most affected contiguous audiometric test frequencies identified at baseline.

The 3 most affected contiguous audiometric test frequencies are the reference and will remain fixed for all further calculations. They are defined according to the unaffected contralateral ear or values of a pre-existing audiogram dated less than 2 years.

At baseline, if 2 or more sequences of 3 contiguous frequencies are similarly affected, the index sequence with the lower contiguous frequencies will be selected as the reference.

If one of the frequency is missing for post baseline values, the PTA will be determined on 2 out of the 3 identified frequencies. If more than 1 is missing, the PTA will not be calculated.

## 13.5 Statistical methods

### 13.5.1 Analysis of primary efficacy endpoint

Mean changes from baseline of the PTA at days 7, 14 and 28 will be analyzed using a restricted maximum likelihood (REML)-based repeated measures approach.

Analyses will include the categorical, fixed covariates of site category (non-ancillary, ancillary), duration of disease and oral corticosteroids intake at baseline (stratification factors) and the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit 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 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.

The estimations and standard errors of the contrasts of interest will be derived from this model. The primary comparison(s) to placebo will be the ones at week 4 ; the comparisons to placebo at the other visits being seen as secondary.

The comparison(s) to placebo at week 4 in the 2 interim GST looks and the final analysis of Part 1 will be performed at the pre-specified significance level attached to each analysis as described later in this section.

**Possible changes during Part 1**

1-Before the interim analysis a blinded examination of the variance of the primary efficacy endpoint will be conducted and compared to the assumption used in planning the study. If this comparison suggests the initial assumption was not optimized, a change in the study sample size will be considered. This possible change will be decided before the first GST look is performed.

2-In the absence of literature results, the pre-specified list of covariates used in the main analysis is not justified from clinical findings. To avoid multi-linearity between covariates, a blind examination of the correlation between the pre-specified covariates and the main endpoint may allow to remove covariates without association with the main endpoint, and simplify the model.

3-During this same blinded examination, the distribution of the D28 primary endpoint data (residuals and predicted value, from a simplified model of D28 data including D0 data as one of the covariates) will also be graphically inspected to determine whether a logarithmic transformation of the data would be appropriate. If such a transformation is retained, the statistical analysis plan will be amended accordingly before the interim analysis.4-Two interim GST looks will be performed during Part 1 of the study, which may lead to early discontinuation of Part 1 for futility or efficacy.

The GST design was defined with a 75% power for a standardized difference of means of 0.546 (15/26.79), an overall 5% one-sided significance level (with a gamma function of parameter -2 as alpha spending function) and a binding futility procedure (with a gamma function of parameter -4 as beta spending function). At each GST look, the z-score statistic will be calculated for the estimated difference of high dose versus placebo. The GST looks are planned for 41 (first GST look), 55 (second GST look) and 74 (final analysis of Part 1) patients available for the high dose and the placebo together. The GST design can be summarized as follows:

| Analysis stage | Futility | | Efficacy | |
|---|---|---|---|---|
| Anticipated cumulative number of subjects in high dose + placebo | nominal p-value limit | z-score limit | nominal p-value limit | z-score limit |
| N = 41 | ≥ 0.6345 | ≤ 0.344 | ≤ 0.075 | ≥ 2.432 |
| N = 55 | ≥ 0.8047 | ≤ 0.859 | ≤ 0.150 | ≥ 2.170 |
| N = 74 | ≥ 0.9500 | ≤ 1.645 | ≤ 0.0500 | ≥ 1.645 |

In this GST design, the first interim look, second interim look and final analysis are planned when 63, 85 and 111 patients, respectively (when 41, 55, 74 patients can be expected in the high dose and placebo groups) have been randomized up to the date still theoretically compatible with reaching Day 28 and having the data centrally reviewed before he considered GST look. However, irrespective of the actual number of patients in high dose and placebo observed in the GST look, the z-score limits for futility and efficacy will be used without any change.

**Final analysis of Part 1**

If the comparison of the high dose versus placebo has been found statistically significant at the last (possibly interim) GST look performed, the comparison of the low dose to placebo will be tested at 5% one-sided significance level; otherwise the 5% one-sided p-value of the comparison of low dosetodose placebo will be considered exploratory.

**Analysis of Part 2**

The efficacy analysis of Part 2 will consider only the data of the patients enrolled in Part 2 and assigned to placebo or to the selected dose. The comparison of the two treatment groups (selected dose, placebo) will be performed at the 5% (two-sided) significance level.

**Combined analysis of Part 1 and Part 2**

A meta-analysis combining all data from Part 1 and Part 2 will be performed.

### 13.5.2 Analysis of secondary efficacy endpoints

Mean changes from baseline in pure tone audiometry (average of the hearing threshold of the 2 most affected hearing frequencies identified at baseline) in affected ear will be analysed using the same modeling approach as for the primary endpoint, but reporting estimates with unadjusted p-values.

Mean changes from baseline in pure tone audiometry (the most affected hearing frequencies identified at baseline) in affected ear will be analysed using the same modeling approach as for the primary endpoint, but reporting estimates with unadjusted p-values.

Mean changes from baseline of the speech recognition threshold at Days 7, 14, 28 and 84 will be analysed using the same modeling approach as for the primary endpoint, but reporting estimates with unadjusted p-values.

Mean changes from baseline of the severity of tinnitus (assessed numerical rating scale) at Days 7, 14, 28 and 84 will be analysed using the same modelling approach as for the primary endpoint, but reporting estimates with unadjusted p-values.

### 13.5.3 Analysis of exploratory efficacy endpoints

The analyses planned for the exploratory efficacy endpoints will be detailed in the statistical analysis plan.

### 13.5.4 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.

#### 13.5.4.1 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 randomised 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 randomised 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 randomised 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.

#### 13.5.4.2 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 test parameter.

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

#### 13.5.4.3 Vital signs

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

#### 13.5.4.4 ECG

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

#### 13.5.4.5 Columbia-Suicide Severity Rating Scale

A descriptive analysis will be performed.

# 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, and the GCP 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/IEC, 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/She will be given a copy of the information leaflet and consent form.

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

The Investigator (or authorized person) 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 (or authorized person) 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.

## 14.4 Regulatory Authority Approval

Before the trial is initiated at a site, the Sponsor will obtain approval to conduct the trial from the appropriate regulatory authority in accordance with applicable country-specific regulatory requirements.

Before starting the pivotal part of the study, the sponsor will submit a substantial amendment to competent authorities for approval of the dose finally selected and sample size. The informed consent form will be updated with the safety information gained from part 1 and the new dose and sample size.

## 14.5 End of the Trial

The end of the entire trial will be defined as the date of the last subject last visit. This provides for a single and conservative definition across all trial sites.

## STUDY MONITORING

### 14.6 Responsibilities of the Investigator

The Investigator undertakes to perform the study in accordance with this protocol, GCP, data protection 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.

The Investigator agrees to complete all information requested in the e-CRF 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 central data management group 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.

### 14.7 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, quality management, integrity and validity of the data recorded on the Case Report Forms. Thus, the main duty of the CRO/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.

### 14.8 Source documents and Data protection

According to the ICH guidelines on GCP, the Monitoring Team must verify the Case Report Form entries against the source documents, except for the pre-identified source data directly recorded in the Case Report Form. The patient will authorize the Sponsor’s duly authorized personnel or CRO, the Ethics Committee (IRB/IEC), and the regulatory authorities to access directly to source documents, in case of audit or specific request to verify any source data which justify the data captured on the Case Report Forms (e.g. subject's medical file, appointment

books, original laboratory records, etc.). The Informed Consent Form will include such a statement.

Subject age, race and ethnicity will be collected in this study as this is required by several health authorities (FDA in the US on African-American, or Hispanics, PMDA: Japanese population in Japan).

### 14.9 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 substantial 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.

The Sponsor will request prior approval by the regulatory and ethics committee all amendments that are considered substantial and likely to have an impact on the safety of the trial subjects or conduct of the study unless there are overriding safety reasons. Non-substantial amendments will be filed in the TMF and the regulatory and ethics committee notified.

# 15 ADMINISTRATIVE RULES

## 15.1 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 [with the exception of Germany] and Financial Disclosure Form study under an IND) will be provided to the Sponsor prior to the beginning of the study and after any changes and end of study.

## 15.2 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 least 15 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.

## 15.3 Confidentiality

The current protocol and any unpublished document referring to SENS-401 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 and data obtained from this clinical trial. Personal data should be treated with the same degree of vigilance as confidential information and in accordance with applicable regulations, including the General Data Protection Regulation n ° 2016/679 ("GDPR").

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 and investigational staff member 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 authorize the sponsor to participate at this audit.

## 15.4 Ownership of data and use of the study results

The data collected in this study will be used only for the purpose of the study and to document the benefit/risk ratio of the investigational product. They may be further processed if they have been anonymized.

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 investigational product tested in this clinical trial, 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 only 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 deadline for submission. Sensorion may request to add the sponsor's name or the name of some employees on the manuscript.

Study results will be made public according to local law.

### 15.5 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.

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

### 15.6 Premature discontinuation of the study or premature close out of a center

#### 15.6.1 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.
- Discontinuation recommended by the DMC after the GST looks in case of futility or because of efficacy of the highest tested dose (see Statistical ConsiderationsConsiderations)
- Unexpected events that could jeopardize the conduct and quality of the study. These events could be any of the followings: Conflicts in a specific country, Major climatic reasons or earthquakes, Unexpected epidemics (eg. SRAS), Financial issues (funding does not match the incurring costs), External constraints that could prevent IMP distribution etc.…External events not yet identified.

In any case, the exact reason of termination will be specified and the ethics committee informed within 15 days after the decision is taken. The health authorities will be informed as soon as possible but not later than 15 days after the decision taken.

#### 15.6.2 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.

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# 17 APPENDICES

### Appendix 1: THE TINNITUS FUNCTIONAL INDEX

*Meikle MB, Henry JA, Griest SE, Stewart BJ, Abrams HB, McArdle R, Myers PJ, Newman CW, Sandridge S, Turk DC, Folmer RL, Frederick EJ, House JW, Jacobson GP, Kinney SE, Martin WH, Nagler SM, Reich GE, Searchfield G, Sweetow R, Vernon JA. (2012) The Tinnitus Functional Index: Development of a New Clinical Measure for Chronic, Intrusive Tinnitus. Ear Hear 33(2):153–176.*

Today's Date
Month / Day / Year

Your Name
Please Print

Please read each question below carefully. To answer a question, select ONE of the numbers that is listed for that question, and draw a CIRCLE around it like this: 10% or 1 .

| I Over the PAST WEEK... |
|---|
| 1. What percentage of your time awake were you consciously AWARE OF your tinnitus?<br>Never aware 0% 10% 20% 30% 40% 50% 60% 70 80% 90% 100% Always aware<br>2. How STRONG or LOUD was your tinnitus?<br>Not at all strong or loud 0 1 2 3 4 5 6 7 8 9 10 Extremely strong or loud<br>3. What percentage of your time awake were you ANNOYED by your tinnitus?<br>None of the time 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% All of the time |
| SC Over the PAST WEEK |
| 4. Did you feel IN CONTROL in regard to your tinnitus?<br>Very much in control 0 1 2 3 4 5 6 7 8 9 10 Never in control<br>5.How easy was it for you to COPE with your tinnitus?<br>Very easy to cope 0 1 2 3 4 5 6 7 8 9 10 Impossible to cope<br>6. How easy was it for you to IGNORE your tinnitus?<br>Very easy to ignore 0 1 2 3 4 5 6 7 8 9 10 Impossible to ignore |
| C Over the PAST WEEK... |
| 7. Your ability to CONCENTRATE?<br>Did not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interfered<br>8. Your ability to THINK CLEARLY?<br>Did not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interfered<br>9. Your ability to FOCUS ATTENTION on other things besides your tinnitus?<br>Did not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interfered |
| SL Over the PAST WEEK... |
| 10. How often did your tinnitus make it difficult to FALL ASLEEP or STAY ASLEEP?<br>Never had difficulty 0 1 2 3 4 5 6 7 8 9 10 Always had difficulty<br>11. How often did your tinnitus cause you difficulty in getting AS MUCH SLEEP as you needed?<br>Never had difficulty 0 1 2 3 4 5 6 7 8 9 10 Always had difficulty<br>12. How much of the time did your tinnitus keep you from SLEEPING as DEEPLY or as PEACEFULLY as you would have liked?<br>None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time |
| A Over the PAST WEEK, how much has your tinnitus interfered with... |

| | Completely interfered | Did not interfere |
|---|---|---|

| | |
|---|---|
| 13. Your ability to HEAR CLEARLY ? | 0 1 2 3 4 5 6 7 8 9 10 |
| 14. Your ability to UNDERSTAND PEOPLE who are talking? | 0 1 2 3 4 5 6 7 8 9 10 |
| 15. Your ability to FOLLOW CONVERSATIONS in a group or at meetings? | 0 1 2 3 4 5 6 7 8 9 10 |
| R Over the PAST WEEK, how much has your tinnitus interfered with... | |
| | Completely interfered ... Did not interfere |
| 16. Your QUIET RESTING ACTIVITIES? | 0 1 2 3 4 5 6 7 8 9 10 |
| 17. Your ability to RELAX? | 0 1 2 3 4 5 6 7 8 9 10 |
| 18. Your ability to enjoy "PEACE AND QUIET"? | 0 1 2 3 4 5 6 7 8 9 10 |
| Q Over the PAST WEEK, how much has your tinnitus interfered with... | |
| | Completely interfered ... Did not interfere |
| 19. Your enjoyment of SOCIAL ACTIVITIES? | 0 1 2 3 4 5 6 7 8 9 10 |
| 20. Your ENJOYMENT OF LIFE? | 0 1 2 3 4 5 6 7 8 9 10 |
| 21. Your RELATIONSHIPS with family, friends and other people? | 0 1 2 3 4 5 6 7 8 9 10 |
| 22. How often did your tinnitus cause you to have difficulty performing your WORK OR OTHER TASKS, such as home maintenance, school work, or caring for children or others? | Never had difficulty 0 1 2 3 4 5 6 7 8 9 10 Always had difficulty |
| E Over the PAST WEEK... | |
| 23. How ANXIOUS or WORRIED has your tinnitus made you feel? | Not at all anxious or worried 0 1 2 3 4 5 6 7 8 9 10 Extremely anxious or worried |
| 24. How BOTHERED or UPSET have you been because of your tinnitus? | Not at all bothered or Upset 0 1 2 3 4 5 6 7 8 9 10 Extremely bothered or upset |
| 25. How DEPRESSED were you because of your tinnitus? | Not at all depressed 0 1 2 3 4 5 6 7 8 9 10 Extremely depressed |
| | |

# INSTRUCTIONS FOR SCORING THE TINNITUS FUNCTIONAL INDEX (TFI)

## 1. Preparation for scoring:

A. **Two items to be transformed**: Items #1 and #3 require a simple transformation from a percentage scale to a 0-10 scale, achieved by dividing the values circled by the respondent by 10. The examiner should write the transformed value in the margin beside the relevant item, preferably using ink of a different color than that used by the respondent.
B. **Ambiguous items**: Because respondents differ in regard to how clearly they circle or mark their answers on the 0-10 scale for each item, the examiner should review every item to resolve any ambiguities. It is helpful if examiners note their decision about each answer in the margin beside the given item, using the differently-colored ink. Some commonly-occurring ambiguities and how to handle them are as follows:

(1) More than one value marked on the 0-10 scale for a given item—
Typically done by respondents whose tinnitus undergoes large variations over time. The clinic or the examiner should settle on a consistent procedure for all such responses, such as (a) averaging the multiple values indicated for a given item, or (b) marking the item "cannot code", thus removing that item from consideration in the overall TFI score. (The latter choice reduces the information available for calculating the respondent's overall score, and may be desirable only in extremely variable cases where the respondent's reliability is questionable.)
(2) Respondent marks a value between the 0-10 values on the item scale—
Again, the clinic or the examiner should settle on a consistent procedure for handling all such ambiguous responses in the same way, such as (a) noting a value of 3.5 in the margin, for a respondent who marked the scale between 3 and 4, or (b) collapsing the intermediate value either to the right (to 4) or to the left (to 3).
(3) Respondent does not make any response to a given item—
The clinic or examiner should decide beforehand how they will indicate missing values, and that notation (e.g. "NA" for "No Answer") should be entered in the margin. If the data will be entered into a computer database, a standard missing value such as "99" can be entered in the margin beside the relevant item. Of course, care must be taken to exclude "99" values if the examiner performs a manual calculation of the overall TFI score. C. Unambiguous items: To facilitate rapid scanning and summing of all valid answers to obtain the respondent's overall TFI score, all of the unambiguous values indicated by the respondent should also be noted in the margin, each such value beside its corresponding item. The examiner can then quickly generate a valid score for the overall TFI.

**2. Calculation of overall TFI score**

(1) Sum all valid answers from both TFI pages (maximum possible score = 250 if the respondent were to rate all 25 TFI items at the maximum value of 10).
(2) Divide by the number of questions for which that respondent provided valid answers (yields the respondent's mean item score for all items having valid answers).
(3) Multiply by 10 (provides that respondent's overall TFI score within 0-100 range).

**CAUTION**—Overall TFI score is not valid if respondent omits **7 or more items**. To be valid as a measure of tinnitus severity, the respondent must answer **at least 19 items** (76% of items).

3. Calculation of subscale scores
The 8 subscales address 8 important domains of negative tinnitus impact as indicated below. Each subscale has a brief title (in capital letters) and a 1- or 2-letter abbreviation (e.g. I for Intrusive, SC for Sense of Control):

| SUBSCALE NAME (and conceptual content) | ITEMS IN SUBSCALE |
|---|---|
| I: INTRUSIVE (unpleasantness, intrusiveness, persistence) | #1, #2, #3 |
| SC: SENSE OF CONTROL (reduced sense of control) | #4, #5, #6 |
| C: COGNITIVE (cognitive interference) | #7, #8, #9 |
| SL: SLEEP (sleep disturbance) | #10, #11, #12 |
| A: AUDITORY (auditory difficulties attributed to tinnitus) | #13, #14, #15 |
| R: RELAXATION (interference with relaxation) | #16, #17, #18 |
| Q: QUALITY OF LIFE (QOL) (quality of life reduced) | #19, #20, #21, #22 |
| E: EMOTIONAL (emotional distress) | #23, #24, #25 |

Each of the 8 subscales consists of 3 items except for the Quality of life subscale, which consists of 4 items (SEE ITEMS LIST ABOVE).

For valid subscale scores, no more than 1 item should be omitted.

Computation of subscale scores is as follows:
1) Sum all of that respondent's valid answers for a given subscale.
2) Divide by the number of valid answers that were provided by that respondent for that subscale.
3) Multiply by 10. For the respondent in question, this procedure generates a subscale score in the range 0- 100 for each valid subscale.

**CAUTION**—Do not attempt to compute a respondent's overall TFI score by combining that respondent's valid subscale scores, as the valid subscales may encompass a total number of items that is different from the number of items accepted as valid for the overall TFI score.

## Appendix 2: EQ-5D-5L

EQ-5D-5L (UK English sample version)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**

| | |
|---|---|
| I have no problems in walking about | ☐ |
| I have slight problems in walking about | ☐ |
| I have moderate problems in walking about | ☐ |
| I have severe problems in walking about | ☐ |
| I am unable to walk about | ☐ |

**Self-Care**

| | |
|---|---|
| I have no problems washing or dressing myself | ☐ |
| I have slight problems washing or dressing myself | ☐ |
| I have moderate problems washing or dressing myself | ☐ |
| I have severe problems in washing or dressing myself | ☐ |
| I am unable to wash or dress myself | ☐ |

**Usual Activities** (e.g. work, study, housework, family or leisure activities)

| | |
|---|---|
| I have no problems doing my usual activities | ☐ |
| I have slight problems doing my usual activities | ☐ |
| I have moderate problems doing my usual activities | ☐ |
| I have severe problems doing my usual activities | ☐ |
| I am unable to do my usual activities | ☐ |

**Pain/Discomfort**

| | |
|---|---|
| I have no pain or discomfort | ☐ |
| I have slight pain or discomfort | ☐ |
| I have moderate pain or discomfort | ☐ |
| I have severe pain or discomfort | ☐ |
| I have extreme pain or discomfort | ☐ |

**Anxiety/Depression**

| | |
|---|---|
| I am not anxious or depressed | ☐ |
| I am slightly anxious or depressed | ☐ |
| I am moderately anxious or depressed | ☐ |
| I am severely anxious or depressed | ☐ |
| I am extremely anxious or depressed | ☐ |

## Appendix 3: 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 occlusion1
- 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
- Cap, diaphragm or sponge with spermicide

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.

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

## Appendix 4: List of commonly prescribed ototoxic treatments

| Class | INN | Class | INN |
|---|---|---|---|
| **Antibiotics** | | **Cytotoxic** | |
| Aminoglycosides – | Amikacin<br>Gentamycin<br>Netilmycin<br>Tobramycin | Vinca alkaloid and etoposide | Etoposide.<br>Vinblastine<br>Vincristine<br>Vindesine<br>Vinorelbine |
| Macrolides | Azithromycin<br>Clarithromycin.<br>Erythromycin | Platinum derivatives | Carboplatin<br>Cisplatin<br>Oxaliplatin |
| Tetracyclines | Minocycline | | |
| Other antibiotics – | Teicoplanin<br>Vancomycin<br>Streptomycin | | |
| **Antiviral** | | **Antimalarial drugs** | |
| | Ganciclovir | | Chloroquine<br>Hydroxichloroquine sulphate |
| **Antifungal** | | Diuretics | |
| | Amphotericin B | Loop diuretic | Furosemide<br>Torsemide |

This list is not exhaustive. In case of doubt, please refer to the labeling of the compound.

## Appendix 5: List of raw data

Study data which should be included in the source dossier:

- Subject's identity and contact detail
- Pathology studied, date of onset of SSNHL and associated symptoms.
- 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: blood pressure, heart rate,
  ⇒ Questionnaires scores including but not limited to TFI, QOL, C-SSRS, vertigo and tinnitus NRS, Tinnitus diary etc
- Adverse events (+ follow-up).
- Pure tone audiometry results and speech recognition threshold and WRS
- Date of drop-out and reason.
- Pregnancy test results
- Laboratory test results
- ECG
- Dates of IP administration, IP non-administration, and rescue medication delivery and compliance
- Patients diary

## Appendix 6: AAO-HNS guidelines

The guidelines published by the AAO-HNS* recommend prednisone for patients with SSNHL within 2 weeks after the diagnosis, with a recommended dose of Prednisone 1 mg/kg/day (max: 60 mg/day), or Methylprednisolone 48 mg/d or Dexamethasone 10 mg/d given as a single dose for 7-14 days, then taper over similar time period.

Intratympanic corticosteroids are recommended as salvage (rescue) after systemic treatment fails. The recommended dose regimen is Dexamethasone 24 mg/mL or 16 mg/mL (compounded), or 10 mg/mL (stock) Methylprednisolone 40 mg/mL or 30 mg/mL with a 0.4 to 0.8 mL injected into middle ear space every 3 to 7 days for a total of 3 to 4 sessions

| | Anti-inflammatory activity | Minéralo-corticoïd Activity | Dose Equivalence | Biological half life |
|---|---|---|---|---|
| Prednisone/Prednisolone* | 4 | 0.8 | **5 mg** | 12-36 |
| Méthylprednisolone | 5 | 0.5 | **4 mg** | 12-36 |
| Dexamethasone | 25 | 0 | **0.75 mg** | 36-54 |

*Reference: Stacler and al. 2012

## Appendix 7: non-exhaustive list of serotoninergic agents

- **Selective serotonin reuptake inhibitors (SSRIs),** antidepressants such as citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline
- **Serotonin and norepinephrine reuptake inhibitors (SNRIs),** antidepressants such as trazodone, duloxetine and venlafaxin
- **Bupropion,** an antidepressant and tobacco-addiction medication
- **Tricyclic antidepressants,** such as amitriptyline and nortriptyline
- **Monoamine oxidase inhibitors (MAOIs),** antidepressants such as isocarboxazid and phenelzine
- **Anti-migraine medications** such as triptans, carbamazepine and valproic acid
- **Pain medications** such as opioid pain medications including codeine, fentanyl, hydrocodone meperidine, oxycodone and tramadol
- **Lithium**, a mood stabilizer
- **Illicit drugs,** including LSD, Ecstasy, cocaine and amphetamines
- **Herbal supplements,** including St. John's wort, ginseng and nutmeg
- **Over-the-counter cough and cold medications** containing dextromethorphan
- **Anti-nausea medications** such as granisetron, metoclopramide, droperidol and ondansetron
- **Linezolid**, an antibiotic
- **Ritonav**, an anti-retroviral medication used to treat HIV/AIDS

## Appendix 8: Clinical inhibitors for transporters

**Examples of clinical inhibitors for transporters (for use in clinical DDI studies and drug labeling) (9/26/2016)**
(https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table5-2)

| Transporter | Gene | Inhibitor |
|---|---|---|
| P-gp | *ABCB1* | amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil |
| BCRP | *ABCG2* | curcumin, cyclosporine A, eltrombopag |
| OATP1B1, OATP1B3 | *SLCO1B1, SLCO1B3* | atazanavir and ritonavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir and ritonavir, rifampin (single dose), simeprevir |
| OAT1, OAT3 | *SLC22A6, SLC22A8* | p-aminohippuric acid (PAH), probenecid, teriflunomide |
| MATE1, MATE2-K | *SLC47A1, SLC47A2* | cimetidine, dolutegravir, isavuconazole, ranolazine, trimethoprim, vandetanib |