Statistical Analysis Plan

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

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1 INTRODUCTION

This document details the planned statistical analyses for Sensorion, protocol "SENS 401-201" study titled "A two-part, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of SENS-401 in subjects with severe or profound sudden sensorineural hearing loss". This document covers the analyses planned for the clinical study reports; one for each part of the study (Part 1 and Part 2). The use of a group sequential test during part 1 is described in section 7 of this document and further detailed in a separate statistical analysis plan (Group Sequential Test SAP). The safety analyses and the efficacy analysis of Part 1 (when all patients have completed or prematurely discontinued the 4-week treatment period) conducted for the Data Monitoring Committee are detailed in a separate statistical analysis plan (Data Monitoring Committee SAP version 1.1 dated 26-NOV-2021).

The proposed analyses are based on the contents of the amended version of the protocol (v4.0 dated 05-FEB-2021).

The study is a 2- part, multicenter, double-blind, randomized, 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/day and 43.5 mg/day (respectively 20 mg and 30 mg free base) will be tested, whereas in the second part only the dose that demonstrated efficacy in part 1 will be tested. The selection of the dose will be done by the Data Monitoring Committee (DMC) when all patients have completed 28 days of treatment in part 1.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

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

3 ENDPOINTS

3.1 Primary 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 on pure tone audiometric air conduction testing) in affected ear from baseline to the end of treatment visit (Visit D28 ± 3).

3.2 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 frequency identified at study entry) in affected ear from baseline to the end of treatment visit (Visit D28± 3)
- 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 on pure tone audiometric air conduction testing) in affected ear from baseline to the end of study visit (Visit D84 ± 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

3.3 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)
- % 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 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

- Change in biomarkers
- Change in EQ-5D-5L scores between baseline and Day 28 and 84
- Change in Distortion Products Otoacoustic Emissions (DPOAE) at Days 7, 14, 28, and 84 compared to baseline values
- Change in Transient Evoked Otoacoustic Emissions (TEOAE) at Days 7, 14, 28 and 84 compared to baseline values

4 SAMPLE SIZE

The sample size is based on the primary endpoint: average change in 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 75%.
- Randomization 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 (with 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 group sequential test (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 SSNHL1 than with the 20dB seen in the publication used at time of the protocol initiation2. 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. The second GST look was not performed because all amendment protocol approvals were not obtained yet at time when the sample size of the second GST was reached. The final look will finally not be performed as it does not have enough added value compared to the analysis planned in the DMC SAP section 2.6.

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%
- Randomization 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 was not revised at time of the amendment for protocol version 4.0 but will be re-estimated based on Part 1 results when available. The final sample size will be submitted for approval to competent authorities prior to the pivotal part start.

5 RANDOMIZATION

Subjects will be randomized to receive one of the treatments (SENS 29 mg dose, SENS 43.5 mg dose, Placebo) according to relevant randomization list (non-ancillary study sites and ancillary study sites). The randomization lists will be stratified according to the duration of the hearing loss (≥24 hours or <24 hours) and the intake of oral corticosteroids (Yes, No). Two randomization lists using a 1:1:1 randomization 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. These two randomization lists will cover both Parts 1 and 2 of the study.

During Part 1, the 3 treatment arms will be allocated by the IWRS. After dose selection at the end of Part 1, only the placebo and the selected active dose (43.5 mg or 29 mg) will be allocated by the IWRS during Part 2.

The randomization lists will be generated centrally, and the investigator, the sponsor study team, the CRO and subjects will be blinded to the Investigational drug administration.

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

Investigators will have no access to the randomization code except under special circumstances. In case of an emergency, when knowledge of the randomization status is deemed necessary for the medical care of the patient, the randomization code can be unblinded for a specific patient (see section 11.3.4 of protocol).

A patient cannot be randomized more than once during the study.

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

6 PLANNED ANALYSES

No statistical analysis plan (SAP) prepared in advance of the data can be absolutely definitive and the final Clinical Study Report (CSR) may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final CSR.

The analysis of Part 1 will include only patients of Part 1. Meanwhile, the analysis of Part 2 will include only patients of Part 2.

6.1 Analysis Sets

Subjects excluded from the analysis sets and the reason for their exclusion will be listed in Appendix 16.2 of the CSR.

6.1.1 Intent-To-Treat Analysis Set

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

6.1.2 Per-Protocol Analysis Set

The Per-Protocol (PP) analysis set will comprise all patients of the ITT analysis set without major protocol deviation, which could affect the analysis of the primary efficacy endpoint. Selected

efficacy analyses (primary efficacy endpoint and secondary endpoints) will be repeated on the PP analysis set.

All protocol deviations will be assessed and documented on a case-by-case basis before the database lock, and deviations considered to have a serious impact on the efficacy results will lead to the relevant subject being excluded from the PP analysis set. Before the soft database lock, that is, when all subjects have completed (or prematurely discontinued) the 4 week treatment period, potential subject exclusions from the PP analysis set will be reviewed by the Sponsor and documented in a subject evaluability document.

6.1.3 Safety Analysis Set

The Safety analysis set will comprise all treated patients. Subjects will be analyzed based on the treatment actually received. In the situation of accidental dispensation of two or three distinct treatments to the same patient, the patient will be counted for the whole study on the highest dose received.

6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.2.1 Race

Where more than one race category has been selected for a subject, these race categories will be combined into a single category labeled “Multiple” in the summary tables. The listings will reflect the original selected categories.

6.2.2 Baseline

Baseline for efficacy is defined as the last non-missing value (either scheduled, unscheduled or repeat) up to the randomization day included but before randomization date and time. According to the protocol, no data are expected to be collected between the randomization and the first intake of study drug.

Baseline for safety is defined as the last non-missing value (either scheduled, unscheduled or repeat) up to the date of first dose of study drug.

6.2.3 Duration / Treatment Day / Study Day

Treatment day, which is to be used for safety analyses, will be calculated as the number of days from first dose of study drug:

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose

Study day, which is to be used for efficacy analyses, will be calculated as the number of days from date of randomization:

- date of event – date of randomization + 1, for events on or after randomization
- date of event – date of randomization, for events before randomization

6.2.4 Conventions for Missing and Partial Dates

All rules explained below for partial / missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual subject listings will be as recorded on the eCRF (i.e., not completed as per the below rules).

6.2.5 Missing / Partial Start / Stop Date of Adverse Events (AE) and Concomitant Medications

Missing and partial start and stop date will be imputed for analysis purposes as follows.

Partial or missing stop date will be imputed as follows:

If the stop date is completely missing and the event has resolved, or the subject has stopped taking the concomitant medication, the stop date will be imputed as the date of the subject's last clinic visit in the study.

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the subject's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the subject's last clinic visit in which case the date of subject's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.

- If the stop date occurs before the start of study drug, the start date of the event/concomitant medication will be imputed as the subject's screening date or the stop date of the event/concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as "01-Jan" of the same year or the date of the first dose of study drug whichever is latest. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event/concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event/concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.
- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

If the start time is missing it will be imputed only in the case where the start date of the concomitant medication/event corresponds to the date of the first dose of study drug. The time will be imputed as the same time as the first dose of study drug. In all other cases the time will not be imputed.

6.2.6 Missing Last Dates of Study Drug Dosing

If the date of last dose of study drug is completely missing, then the date of last dose of study drug will be taken for analysis purposes as the date when the subject would have run out of study drug assuming full compliance from the date the study drug was last dispensed or the date of subject's last clinic visit in the study or early withdrawal or death whichever the earlier.

If only the month and year of the last dose was recorded, then the date of last dosing will be taken for analysis purposes as the date the subject would have run out of study drug assuming full compliance from the date the study drug was last dispensed, the last day of the month of the recorded last dose or the date of subject's last clinic visit in the study or early withdrawal or death whichever the earlier.

6.2.7 Missing Diagnosis Dates

If the month and year are present but the day is missing, the diagnosis date will be set to first day of the relevant month. If only the year is recorded the diagnosis date will be set as "01-Jan" for that year.

6.2.8 Exposure to Study Drug

Exposure to study drug will be calculated as follows from the date of last dosing minus the first day of dosing + 1. The exposure calculation will not take into account breaks in therapy.

6.2.9 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.2.10 Height/Weight/Temperature

When height is collected in inches (in), the measurements will be converted to centimeters (cm) using the following rule:

Height (cm) = 2.54*height (in)

When weight is collected in pounds (lbs), the measurements will be converted to kilograms (kg) using the following rule:

Weight (kg) = 0.45359237*weight (lbs)

When temperature is collected in Fahrenheit degrees (F), the measurements will be converted to Celsius degrees (C) using the following rule:

Temperature (C) = (temperature (F) – 32)/1.8

6.2.11 Electrocardiogram (ECG) Data

The Banook Group will prepare a separate ECG SAP for the analysis of the ECG data. .

6.2.12 Columbia-Suicide Severity Rating Scale (C-SSRS)

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definition of composite endpoints:

Category 1	Wish to be Dead

Category 2	Non-specific Active Suicidal Thoughts
Category 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Category 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Category 5	Active Suicidal Ideation with Specific Plan and Intent
Category 6	Preparatory Acts or Behavior
Category 7	Aborted Attempt
Category 8	Interrupted Attempt
Category 9	Actual Attempt (non-fatal)
Category 10	Suicidal Behavior (Lifetime and Past 12 Months version) / Suicide (Since Last Visit version)

Suicidal Ideation at baseline – A "yes" answer at baseline to any one of the 5 suicidal ideation questions (categories 1-5) on the C-SSRS Lifetime or Past 12 Months version.

Suicidal Behavior at baseline – A "yes" answer at baseline to any one of the 5 suicidal behavior questions (categories 6-10) on the C-SSRS Lifetime or Past 12 Months version.

Suicidal Ideation since baseline – A "yes" answer at any time during double blind treatment to any one of the 5 suicidal ideation questions (categories 1-5) on the C-SSRS Since Last Visit version.

Suicidal Behavior since baseline – A "yes" answer at any time during double blind treatment to any one of the 5 suicidal behavior questions (categories 6-10) on the C-SSRS Since Last Visit version.

There will be no imputation of missing data for C-SSRS.

6.2.13 Laboratory data

The following rules will be applied for purposes of unit conversion of WBC differential parameters:

Result value (10^9/L) = Result value (%) * WBC (10^9/L)

Ref Range value (10^9/L) = Ref Range value (%) * WBC Ref Range value (10^9/L) min and max

6.2.14 Randomization Strata

The randomization will be stratified according to the site category (non-ancillary, ancillary), the duration of the hearing loss (≥ 24hours/< 24 hours) and the intake of corticosteroids (Yes, No).

6.2.15 Change from baseline

Change from baseline in absolute terms is defined as the baseline value subtracted from the postbaseline value.

6.2.16 Analysis Window

For the analysis of all the efficacy and safety endpoints, the following analysis windows will be used to obtain the analysis visits. For each respective analysis visit, all assessments, either scheduled or unscheduled/repeat, will be considered. The values collected during the study will be mapped to protocol visits according to the windowed times indicated below. Should more than one value fall within the same time window, then the closest value to the planned day will be assigned to the visit. If the values are equidistant to the planned day, the latest value will be retained.

Analysis Visit	Window
Day 7	[Day 5, Day 9] (Day 7 +/- 2 days)
Day 14	[Day 10, Day 18] (Day 14 +/- 4 days)
Day 28	[Day 20, Day 36] (Day 28 +/- 8 days)
Day 84	[Day 60, Day 108] (Day 84 +/- 24 days)

Note: Day in the table is Study Day for efficacy endpoints, Treatment Day for safety endpoints

6.3 Conventions

All data listings, summaries, figures and statistical analyses will be generated using SAS version 9.4 or higher[3].

Summaries will be presented by treatment group and/or overall. Treatment group labels will be displayed as follows for Part 1:

SENS 29mg SENS 43.5mg Placebo

For Part 2, treatment group labels will be displayed as follows:

SENS XXmg Placebo

Overall columns are to be included within the table shells as follows:

Data	Columns labels
Demography	Treatment groups and overall
Baseline	Treatment groups and overall
Disposition	Treatment groups and overall
Efficacy	Treatment groups
Pharmacokinetic (PK)	Treatment groups
PD	Treatment groups
AEs	Treatment groups and overall
Other safety	Treatment groups

Listings will be sorted in the following order: treatment group, subject, parameter, and visit, unless otherwise stated. All data will be listed, subjects who were not randomized will be displayed after the randomized treatment groups.

Continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum. For all tabulations of changes from baseline data, the lower and upper 95% confidence limits for the mean for the individual treatments will be given.

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the subject population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

6.3.1 Decimal Places

Decimal places for derived data described in Section 6.2 will be determined by the scale of measurement unless otherwise stated. No decimal places will be displayed if the smallest calculated value is ≥ 100; 1 decimal place will be displayed when the smallest value is within the interval (10, 100), with 10 being inclusive; 2 decimal places will be displayed when the smallest value is within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement.

Derived data where it is known in advance the result will be an integer for example day, month, year, number of days and total scores (for rating scales) will be presented with zero decimal places.

Means, medians and percentiles will be displayed to one more decimal place than the data**,** dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. Percentages will be displayed with one decimal place.

P- Values will be quoted to 4 decimal places. P-values < 0.0001 will be presented as p<0.0001.

6.4 Subject Disposition

For each part of the study, subject disposition will be summarized by center and overall (i.e. across centers) as follows:

- The number of subjects who failed screening and the reasons for failure will be tabulated for all screened subjects.
- The number of subjects randomized, and number of subjects in each analysis set will be summarized by treatment group and overall based on the ITT set.
- The number of early withdrawals and the reason for withdrawals will be tabulated by treatment group and overall based on the ITT set.

6.5 Protocol Deviations

Protocol deviations will be classified as Major, Minor, or Critical. Additionally, any COVID-19-related protocol deviations will be identified. A tabulation of the number of protocol deviations within each classification will be presented by treatment group and overall for the ITT analysis set. A listing of protocol deviations will be provided within Appendix 16.2 of the CSR.

6.6 Stratification factors

For each part of the study, the distribution of the subjects across the categories of each of the 3 stratification factors (site category (non-ancillary, ancillary), duration of disease (< 24 hours, ≥24 hours), and oral corticosteroids intake at baseline (yes, no)), will be summarized by randomized treatment group and overall based on the ITT analysis set.

6.7 Baseline Comparability

The comparability of treatment groups with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

For each part of the study, standard continuous or categorical variable summaries will be presented by randomized treatment group and overall based on the ITT analysis set.

All baseline data will also be listed.

6.7.1 Demographics

The following variables will be summarized:

- age at informed consent (years)
- gender
- fertility status (female subjects)
- ethnicity
- race
- height (cm)
- weight (kg)
- BMI (kg/m^2)

6.7.2 Disease Characteristics and Other Relevant Baseline Data

The following variables will be summarized:

- Duration of current hearing loss episode at time of randomisation (in hours): randomisation date/time-SSNHL onset date/time, continuous and by class (<24 hours, [24; 48[, [48; 72[, >72 hours)
- Cause of current hearing loss/SSNHL: idiopathic, trauma (including noise induced), infectious, otologic disease, ototoxic drug intake, vascular/hematologic, neoplastic
- Oral Corticosteroids (CM.CMCAT = “ORAL STEROID”) for SSNHL (CM.CMINDC = “SSNHL”) at baseline (ongoing or started the day of first study treatment intake): yes/no and type (prednisone/prednisolone, methylprednisolone, dexamethasone or other)
- Otologic history: ear used for telephone and recent switch, professional exposure to very loud noise, recreational exposure to very loud noise, history of severe ear problems (previous SSNHL, frequent otitis media, past history of ear surgery, wearing hearing aids, past history of tinnitus in each ear), ear/head/neck/nose/throat problems (infection, respiratory tract infection, ear pain, ear pressure, otorhea, severe headache or migraine, recent head or neck trauma, recent baro trauma, exposure to loud noise, past otologic evaluation)

- Baseline Pure Tone Audiometry air conduction average of the hearing threshold of 3 contiguous most affected hearing frequencies in decibels as identified at study entry (PTA) for the current hearing loss episode:
    - Initial frequency range (≤ 2000 Hz, > 2000 Hz) derived as the mean between the lowest and the highest of the most affected frequencies
    - Affected ear side (right, left)
    - Affected ear PTA continuous (in decibels)
    - Affected ear PTA by class (<20 dB, ≥20 dB to ≤35 dB, >35 dB to ≤50dB, >50 to ≤70 dB, >70 to ≤90 dB, >90 dB)
    - Reference type (contralateral ear, previous PTA, reference frequency)
    - Reference PTA continuous
    - Reference PTA by class
    - Hearing loss (difference between the PTA on affected ear and the reference PTA for the identified frequencies) continuous (in decibels)
    - Hearing loss by class according to American Speech-Language-Hearing Association criteria (ASHA) (<16, 16 to <26dB, 26 to <41dB, 41 to <56dB, 56 to <71dB, 71 to <91dB, ≥91dB)
- Tinnitus numeric rating scale (NRS) as recorded in the eCRF (XT.XTCAT= "Questionaire"): score (from 0 to 10)
- Vertigo NRS: score (from 0 to 10)
- Speech recognition threshold (SRT) on affected ear: minimum hearing level at which the patient can correctly recognizes 50 % of the presented speech material
- Word recognition score (WRS) also called Speech discrimination score on affected ear: percentage of words correctly repeated at 60dB and 80dB
- Tinnitus functional index (TFI) Total Score (from 0 to 250)

6.8 Medical/Surgical History

For each part of the study, separate tabulations of previous and ongoing medical and surgical conditions at screening will be presented by randomized treatment group and overall, for the ITT analysis set. Conditions will be presented by Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class and preferred term, using the most recent MedDRA version available at the time of database lock.

All data will be listed.

6.9 Prior and Concomitant Medications

For each part of the study, separate tabulations will be produced for prior and concomitant medications presented by randomized treatment group and overall, for the Safety analysis set. Prior medications are defined as all medications that started and stopped before the date of first dose of study drug. Concomitant medications are defined as medications that started prior to, on or after the date of first dose of study drug and ended on or after the date of first dose of study drug or are ongoing at end of study. Prior and concomitant medications will be summarized using Anatomic Therapeutic Chemical (ATC) Level 2. All medications will be coded using the most recent version of the WHO Drug Dictionary available at the time of database lock.

A separate tabulation for study treatment concomitant medications, defined as medications that started before date of the first dose of study drug and continued while on study drug or medications that started between the day of the first dose of study drug (included) and the date of the last dose of study drug (included) will be displayed by randomized treatment group and overall, for the Safety analysis set.

A separate tabulation for prior and concomitant use of oral corticosteroids (excluding use as rescue medication) will be displayed by randomized treatment group and overall, for the Safety analysis set.

A separate tabulation for concomitant corticosteroid as rescue treatment will be tabulated. Supporting dosing information will be listed, along with the other prior and concomitant medications.

6.10 Exposure to Study Drug

Extent of exposure (number of days of exposure to study drug) will be presented by randomized treatment group for the Safety analysis set.

6.11 Treatment Compliance

Overall percent compliance to study drug dosage regimen, calculated as percent doses taken relative to doses scheduled to be taken, that is,

$$\frac{(\text{Total Dispensed} - \text{Total Returned}) \times 100}{3 * 2 * \textit{Extent of exposure to study drug}}$$

where the "Total Dispensed" is 180 and "Total Returned" is the sum of the Blue label, Yellow label, and Green label tablets returned by patient. Subject compliance will be summarized by treatment group for the Safety analysis set.

6.12 Efficacy Analyses

For Part 1 all statistical tests will be performed using a one-tailed 5% significance level. All comparisons between treatments, where high dose vs. placebo will be tested first, and then testing conditionally low dose vs. placebo, will be reported with 90% confidence intervals for the difference.

For Part 2, all statistical tests will be performed using a two-tailed 5% significance level. All comparisons between treatments will be reported with 95% confidence intervals for the difference.

6.12.1 Primary 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) on pure tone audiometric air conduction testing in the affected ear from baseline to the end of treatment visit (Visit D28 ± 3).

The 3 most affected contiguous audiometric test frequencies are defined with respect to the unaffected contralateral ear and will be fixed for all further calculations. In case of a pre-existing contralateral hearing loss, the corresponding values of a pre-existing audiogram of the affected ear, if dating back less than 2 years, will be considered as the reference. For all other scenarios (e.g. pre-existing contralateral hearing loss with no audiogram in the past 2 years) the reference frequencies will be set using the ISO 7029;2017 norm values. 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. If both ears are equally affected, the right ear will be considered.

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. Pure tone average frequencies determined at baseline will remain fixed for all evaluations.

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

6.12.2 Primary Efficacy Analysis

The null and alternative hypotheses for part 1 of the study are as follows, where μ_H, μ_L and μ_P are defined as the mean change in PTA of the high dose, low dose, and placebo respectively:

H_{0H}: $\mu_H - \mu_P = 0$, H_{AH}: $\mu_H - \mu_P < 0$ (greater decrease on high dose)
H_{0L}: $\mu_L - \mu_P = 0$, H_{AL}: $\mu_L - \mu_P < 0$ (greater decrease on low dose)

Analysis of Part 1

To preserve type I error rate during part 1, the above hypotheses will be tested according to a fixed-sequence testing strategy: the comparison of the high dose versus placebo will be tested first at 5% one-sided significance level; then the comparison of the low dose versus placebo will tested at 5% one-sided significance level conditionally to the significance of the high dose. This procedure is compliant with the principle of the closed test procedure (Marcus[4] et al., 1976, Koch[5] 1996). In the event that the null hypothesis H_{0H} cannot be rejected for the high dose, the p-value associated with H_{0L} will still be provided but considered exploratory. The comparison of the high dose versus the low dose will be considered exploratory.

Analysis of Part 2

After completion of Part 1, one dose will be dropped and the other will be carried over to part 2. Hence at the end of part 2 only one null hypothesis will be tested:

H_0: $\mu_T - \mu_P = 0$, H_A: $\mu_T - \mu_P \neq 0$

Where μ_T is the change from baseline in PTA for the active treatment arm of part 2. This hypothesis will be tested at the 5% two-sided significance level.

Analysis details

Descriptive statistics (n, mean, SD, median, Q1, Q3, min, max) of observed data by visit (Day 7, 14, 28) and treatment group (placebo, SENS401 29 mg, SENS401 43.5 mg) displaying baseline, post-baseline, change will be provided.

Mean changes from baseline of the hearing loss at days 7, 14, and 28 will be analyzed using a restricted maximum likelihood (REML)-based repeated measures approach under the assumption of data missing at random (MAR). Analyses will include the categorical, fixed covariates of site category (non-ancillary, ancillary), duration of disease (≥24 hours or < 24 hours), and oral

corticosteroids intake at baseline (yes or no) as entered in the IWRS and the fixed, categorical effects of treatment, visit (Day 7, Day 14, Day 28), and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. An unstructured (UN) covariance structure will be used to model the within-patient errors. If this analysis fails to converge, simpler structures such as first-order ante-dependent ANTE(1), first-order autoregressive AR(1), or compound symmetry (CS) will be tested in a model without treatment effect. The covariance structure converging to the best fit, that is, with the lowest Akaike's information criterion (AIC), 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. For each timepoint the marginal predicted means (Least Squares Means) and corresponding standard error and confidence interval (consistent with the significance level applied for the study part considered) will be displayed (and also graphically illustrated with mean changes on y-axis and time on the x-axis by treatment groups). The p-value of the visit by treatment interaction will be provided. For each timepoint, one-sided p-values for the comparisons with Placebo and for the comparison of high dose versus low dose will also be displayed with comparisons with Placebo at Day 28 being the comparisons of primary interest while the other comparisons are secondary.

SAS code to perform the analysis described above for part 1 (i.e. when 3 treatment arms are available) is provided below wherein TRT01PN is the treatment group, AVISITN is the analysis visit (Day 7, 14, and 28) as defined in Section 6.2.15, ANCIL is the site category (non-ancillary, ancillary), DHR is the duration of the hearing loss (≥24 hours or <24 hours) strata, and CORT is the intake of oral corticosteroids at baseline (Yes, No) strata. Note that the ordering of the coefficients for the ESTIMATE statements may need to be updated depending on the entry order in the CLASS statement and will be different for the analysis of part 2 (where only 2 treatment arms will be present). Moreover, 'TYPE=UN' may need to be replaced with 'TYPE=ANTE(1)', 'TYPE = AR(1), or 'TYPE=CS' if the model with 'TYPE=UN' failed to converge.

```
proc mixed data = <dataset>;
  class subjid trt01pn avisitn ANCIL DHR CORT;
  model chg = trt01pn avisitn trt01pn*avisitn base base*avisitn ANCIL DHR
CORT / ddfm = kr;
  repeated avisitn / type = un subject=subjid(trt01pn);
  lsmeans trt01pn*avisitn / cl e alpha = 0.10;
  estimate 'High vs Placebo, day 28'
           trt01pn -1 0 1
           trt01pn*avisitn 0 0 -1 0 0 0 0 0 1 / alpha = 0.10 cl;
  estimate 'Low vs Placebo, day 28'
```

```
            trt01pn -1 1 0
            trt01pn*avisitn 0 0 -1 0 0 1 0 0 0 / alpha = 0.10 cl;
  estimate 'Low vs High, day 28'
            trt01pn 0 1 -1
            trt01pn*avisitn 0 0 0 0 0 1 0 0 -1 / alpha = 0.10 cl;
run;
```

A similar code (with 2 groups only and alpha = 0.05, two-sided p-value) will be used for the analysis of Part 2.

The number of subjects, the affected ear and the type of reference (unaffected contralateral ear, reference values from a pre-existing audiogram, ISO 2017) will be tabulated by treatment group, stratification groups, and overall.

All PTA data will also be listed.

6.12.3 Sensitivity Analyses

A first sensitivity analysis will assess the impact of major protocol violations to study results, by repeating the primary analysis on the Per Protocol population.

A second sensitivity analysis will further assess the impact of the MAR assumption of the main analysis by imputing missing data at Day 7, Day 14 or Day 28 under control-based multiple imputation framework under the assumption that data are missing not at random (MNAR) and using the Copy Reference (CR) approach (Carpenter[6] 2013). Thus, instead of imputing a single value for each missing observation, a set of values will be generated from the model resulting in as many distinct complete datasets without missing data. The imputation model will include the PTA baseline, the three stratification factors (site category, hearing loss duration and intake of corticosteroids at baseline) and the Day 7, Day 14, Day 28 PTA data. Missing data at Day 7, Day 14, and Day 28 for subjects from all three treatment groups will be imputed using data observed in the placebo group. This approach assumes that patients with missing data in the active treatment groups have outcomes trending towards outcomes observed in the placebo group, i.e., the imputations result in a treatment effect that gradually diminishes towards the placebo group. In a first step "intermittent" missing data (a post-baseline is missing but one or more later assessments are available) will be first imputed by a Markov Chain Monte-Carlo (MCMC) method using a non-informative Jeffrey's prior, thus creating multiple partially imputed "monotone" datasets; then, the remaining missing data will be imputed once in each of the "monotone" imputed datasets using the CR approach leading finally to multiple complete imputed datasets. An analysis of covariance (ANCOVA) will then be used to analyze the change from baseline to Day 28 on each complete

imputed dataset. The following terms will be included in the ANCOVA model: the PTA baseline, the three stratification factors (site category, hearing loss duration and intake of corticosteroids at baseline), and the treatment group. Uncertainty in the imputations will be reflected appropriately in the analysis by combining the results on each imputed dataset using Rubin's methodology.

More specifically, the imputations will be performed in two steps: “intermittent” missing data (a result is missing but one or more results are available at following visits) will be first imputed by a MCMC method using a non-informative Jeffrey’s prior, thus creating 500 partially imputed “monotone” datasets; then, the remaining missing data will be imputed once in each of these 500 “monotone” imputed datasets using the CR approach leading finally to 500 complete imputed datasets.

The two-step MI procedure will be implemented by the following SAS code:

```
proc mi data=<dataset> nimpute=500 seed=32767 min = . . . . . -10 -10 -10
max = . . . . . 120 120 120 minmaxiter = 1000000 out=h2;
 where base ne .;
 mcmc impute = monotone;
 var trt01pn ANCIL DHR CORT base Day07 Day14 Day28;
run;

proc mi data=h2 nimpute=1 seed=32767 min = . . . . . -10 -10 -10  max = . . .
. . 120 120 120 minmaxiter = 1000000 out=h3;
 by _imputation_;
 class trt01pn ANCIL DHR CORT;
 var ANCIL DHR CORT base Day07 Day14 Day28;
 mnar model (Day07 Day14 Day28 / modelobs=(trt01pn = "1"));*"1" = placebo;
 monotone regression;
run;

data h3;
 set h3;
 chg = Day28 - baseline;
run;
```

An analysis of covariance (ANCOVA) model will then be used to analyze this endpoint on each imputed dataset using the following SAS code for Part 1:

```
proc mixed data=h3;
by _imputation_;
 class trt01pn ANCIL DHR CORT;
 model chg = ANCIL DHR CORT base trt01pn / solution;
 lsmeans trt01pn / diff=control("3") cl;*"1" = placebo;
 ods output lsmeans =lsm diffs=lsmdiffs ;
run;
```

Uncertainty in the imputations will be reflected appropriately in the analysis by combining the results on each imputed dataset using Rubin's methodology (Rubin[7] 1987). The final estimate is the mean of the estimates from the 500 imputed datasets, and the final variance is the sum of the average within-imputation variance and (1 + 1 / 500) times the between-imputation variance. From the final point estimate and variance, the 90% CI will be determined. The results aggregation of the MI procedure after analysis of the 500 imputed datasets will be implemented by the following SAS code:

```
proc mianalyze data=lsm alpha=0.10;
 by trt01pn;
 modeleffects Estimate;
 stderr StdErr ;
run;

proc mianalyze data=lsmdiffs alpha=0.10;
 modeleffects Estimate;
 stderr StdErr ;
run;
```

A similar code (with 2 groups only and alpha = 0.05) will be used for the analysis of part 2

A third sensitivity analysis will assess the impact of the use of rescue therapy by repeating the primary analysis after having set to missing all PTA assessments performed after initiation of a rescue therapy and then imputing each missing Day 28 of a subject having received rescue therapy by the subject baseline.

6.12.4 Secondary Endpoints

6.12.4.1 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)

Mean changes from baseline in pure tone audiometry (average of the hearing threshold of the 2 most affected hearing frequencies identified at baseline) on pure tone audiometric air conduction testing in affected ear will be analyzed using the same modeling approach as for the primary endpoint for both study parts. The 2 most affected hearing frequencies will be defined as the first 2 frequencies within the 3 most affected hearing frequencies identified at baseline sorted by descending order of the hearing losses observed at baseline and by increasing order of the frequencies.

Values at each timepoint and their changes from baseline will also be summarized descriptively by treatment group and a line plot of the model estimates of the mean changes from baseline over time by treatment group will be presented.

6.12.4.2 Change in pure tone audiometry (the most affected hearing frequency identified at study entry) in affected ear from baseline to the end of treatment visit (Visit D28± 3)

Mean changes from baseline in pure tone audiometry (the most affected hearing frequency identified at baseline) on pure tone audiometric air conduction testing in affected ear will be analyzed using the same modeling approach as for the primary endpoint for both study parts but without imputation for missing Day 28 results. The most affected hearing frequency will be defined as the first frequency within the 3 most affected hearing frequencies identified at baseline sorted by descending order of the hearing losses observed at baseline and by increasing order of the frequencies.

Values at each timepoint and their changes from baseline will also be summarized descriptively by treatment group and a line plot of the model estimates of the mean changes from baseline over time by treatment group will be presented.

6.12.4.3 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 on pure tone audiometric air conduction testing) in affected ear from baseline to the end of study visit (Visit D84 ± 3)

Mean changes from baseline in pure tone audiometry (average of the hearing threshold of the 3 contiguous most affected hearing frequencies identified at baseline) on pure tone audiometric air conduction testing in affected ear will be analyzed using the same modeling approach as for the primary endpoint for both study parts and expanded by including the Day 84 data in the model.

Values at each timepoint and their changes from baseline will also be summarized descriptively by treatment group and a line plot of the model estimates of the mean changes from baseline.

6.12.4.4 Change in speech discrimination threshold from baseline to Day 28, and 84.

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. Assessments with missing value with "Reason not performed" = "No response due to hearing loss" will be assigned with the maximum observed value in the database.

Mean changes from baseline of the speech recognition threshold at Days 7, 14, 28 and 84 will be analyzed using the same modeling approach as for the primary endpoint for both study parts. A line plot will be produced to show the discrimination threshold by timepoint for each treatment group for all individual subjects.

6.12.4.5 Frequency and severity of tinnitus at Days 7, 14, 28, and 84 assessed by numerical rating scale

Mean changes from baseline of the severity of tinnitus (assessed numerical rating scale) at Days 7, 14, 28 and 84 will be analyzed using the same modeling approach as for the primary endpoint. For Days 7 and 14 the patients diary log data (PM measurements) will be used.

For each relevant timepoint the number and percentage of patients experiencing tinnitus will be tabulated. Severity of reported tinnitus will be summarized as counts and percentages as well on a scale from 0 (no tinnitus) to 10 (extreme tinnitus).

All data on reported tinnitus occurrences and severity will also be listed.

6.12.5 Exploratory Endpoints

All the following endpoints will only be analyzed based on the ITT population. The results will be presented descriptively (with confidence intervals where indicated, 90% confidence intervals for Part 1 data, 95% confidence intervals for Part 2 data).

6.12.5.1 % of patients with complete hearing recovery defined as PTA <20 dB or hearing similar to the unaffected contralateral ear

The proportion of patients with a complete hearing recovery or hearing similar to the unaffected ear will be summarized at Day 28 and Day 84 alongside an exact confidence interval. Hearing in the affected ear will be considered similar to the unaffected one if the absolute difference in pure tone audiometric air conduction testing (average of the hearing threshold of 3 contiguous most affected hearing frequencies in decibels as identified at study entry) is < 5dB, and this rule will also be applied to cases where either an old audiogram was used or normative values were considered as reference (e.g. pre-existing contralateral hearing loss with no audiogram in the past 2 years). Patients with complete hearing recovery are those that have pure tone audiometric air conduction testing (average of the hearing threshold of 3 contiguous most affected hearing frequencies in decibels as identified at study entry) of < 20dB.

6.12.5.2 % of patients with marked improvement defined as PTA threshold absolute improvement > 30 dB

The proportion of patients with marked improvement in pure tone audiometric air conduction testing (average of the hearing threshold of 3 contiguous most affected hearing frequencies in decibels as identified at study entry), that is, PTA at post-baseline minus baseline PTA is > 30dB, will be summarized by treatment group for Day 28 and Day 84 along with an exact confidence interval.

6.12.5.3 % of patients with PTA > 35 dB and > 90 dB on Day 7, Day 14 and end of study visit (visit D84± 3)

The proportion of patients with PTA >35 dB and >90 dB on pure tone audiometric air conduction testing at the given timepoints (Day 7, 14, and 84) will be summarized by treatment group alongside an exact confidence interval. The PTA that will be utilized here is the average of the hearing threshold of 3 contiguous most affected hearing frequencies in decibels as identified at study entry.

6.12.5.4 % of responders (response is defined as an improvement of 10dB or more) in PTA

For this endpoint, a subject will be classified as "responder", that is, if the subject has an improvement of 10dB or more in PTA (pure tone audiometric air conduction testing) from baseline, or "non-responder" otherwise for each timepoint (Day 7, 14, 28, and 84). The PTA that will be utilized here is the average of the hearing threshold of 3 contiguous most affected hearing frequencies in decibels as identified at study entry. The % of responders will be summarized by treatment group at each timepoint alongside an exact confidence interval. In addition, the proportion of responders at each timepoint for each treatment arm will also be graphically represented.

6.12.5.5 Word recognition score at 80 dB and 60 dB in the affected ear on Day 28 and 84

The word recognition score (that is, percent of words correctly repeated) at 80 and 60 dB in the affected ear and its changes from baseline to post-baseline timepoints will be summarized by treatment group using descriptive statistics for continuous variables. In addition, the following graphical displays will be presented:

- Percent change from baseline in Word Recognition Score in the affected ear by dB level over time, with a reference line at 15% to identify the clinically relevant improvement threshold.
- Word Recognition Score for the affected ear over time, by treatment group and dB level
- Difference in Word Recognition Scores between the affected and reference ear over time, by treatment group and dB level

All word recognition data on both ears will be listed.

6.12.5.6 Relationship between time of onset of symptoms to first study drug intake and the primary endpoint

The time of onset of symptoms to first study drug intake (in days) will be obtained as follows:

date of first dose of study drug – date of the onset of SSNHL symptoms and will be summarized descriptively by treatment group.

The relationship between time of onset of symptoms to first study drug intake and the change in PTA at Day 28 from baseline will be explored through a scatter plot along with the Pearson correlation coefficient.

6.12.5.7 Frequency and severity of any vertigo at day 1,7,14, 28 and 84

For each relevant timepoint the number and percentage of patients reporting vertigo will be summarized by treatment group. Severity of reported vertigo episodes will be summarized as counts and percentages as well on a scale from 0 (no vertigo) to 10 (extreme vertigo). The frequency of patients experiencing vertigo will also be displayed graphically for each treatment group and timepoint via a bar chart.

All data on reported vertigo episodes will also be listed.

6.12.5.8 Tinnitus burden based on the change in tinnitus QOL scores at day 1,7,14, 28 and 84

The Tinnitus Functional Index (TFI) comprise of 25 questions on the impact of the tinnitus on the individual behavior and feelings in which items 1 and 3 are in percentage scale, that is, from 0 to 100 with increment of 10 while all the other items are in 0 to 10 scale with an increment of 1. Thus, items 1 and 3 need to be transformed into a 0 to 10 scale by dividing the value by 10 before obtaining the subscale score to which the items belong, as well as the total TFI score. The questionnaire has eight subscales that address the intrusiveness of tinnitus (items 1, 2, 3), the sense of control the patient has (items 4, 5, 6), cognitive interference (items 7, 8 , 9), sleep disturbance

(items 10, 11, 12), auditory issues (items 13, 14, 15), relaxation issues (items 16, 17, 18), quality of life (items 19, 20, 21, 22), and emotional distress (items 23, 24, 25). In obtaining the subscale score, the response to all the items that belong to the corresponding subscale score will be added then divided by the number of items that have responses, and eventually multiplied by 10. Thus, the subscale score would range from 0 to 100. For a valid subscale score, no more than 1 item should have missing response. Otherwise, the subscale score will be set to missing. The TFI total score is obtained by adding the values of all the items that have responses then dividing by the number of items that have responses, and eventually multiplying by 100. TFI total score will range from 0 to 100. For a valid TFI total score, there should be at least 19 items that have non-missing responses. Otherwise, the TFI total score will be set to missing.

The TFI subscale scores and total score, along with the corresponding changes from baseline will be summarized for all the relevant timepoints by treatment group. All responses to TFI items, as well as derived TFI data (total and subscale scores) will be listed.

6.12.5.9 Change in biomarkers

Prestin results and its change from baseline will be summarized descriptively at baseline, Day 14, and Day 28 (EoT).

All biomarker data will be listed.

6.12.5.10 Change in EQ-5D-5L scores between baseline and Day 28 and 84

EQ-5D is a standardize measure of health status that consists of two parts: health-status descriptive system questionnaire which provides a simple descriptive profile of the responder's health, and EQ visual analogue scale (VAS) which is a quantitative measure of the responder's overall health based on his/her own judgement. The descriptive system comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with five response levels (no problems, slight problems, moderate problems, severe problems, unable to/extreme problems). Meanwhile, VAS ranges from 0 to 100 which corresponds to 'worst health you can imagine' to 'best health you can imagine' respectively.

The number of patients reporting each response level for each of the five dimensions will be summarized by treatment group for each baseline and post-baseline visits. Shift tables from baseline to post-baseline visits will also be presented for each dimension. In addition, a summary of dichotomize response, that is, 'no problem' when the response is level 1 ("no problems" or "no pain or discomfort" or "not anxious or depressed") and 'any problems' when the response is level

2 to 5 (any other responses), will be presented by treatment group for the baseline and post-baseline visits.

The EQ Visual Analogue Scale (VAS) and its change from baseline to Day 28 (EoT) and Day 84 (EoS/Follow-up) will be summarized by treatment group.

All EQ-5D-5L data will also be listed.

6.12.5.11 Change in DPOAE at Days 7, 14, 28, and 84 compared to baseline values

The corresponding assessments were optional in the protocol leading to data available in only a small subset of subjects. For each collected variable, descriptive statistics by treatment group and visit will be presented for the affected ear.

6.12.5.12 Change in TEOAE at Days 7, 14, 28 and 84 compared to baseline values

The corresponding assessments were optional in the protocol leading to data available in only a small subset of subjects. For each collected variable, descriptive statistics by treatment group and visit will be presented for the affected ear.

6.12.6 Multiplicity

Multiplicity adjustment for comparing treatment groups in part 1 (3 treatment groups) for a given endpoint is addressed by testing first the high dose versus placebo and then testing the low dose versus placebo conditionally to the significance of the high dose as described in Section 6.12.2. As for the secondary endpoints, analyses will be carried out after the primary endpoint following a sequential testing procedure. The order of testing will be as follows:

1. 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) [primary endpoint]
2. 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)
3. Change in pure tone audiometry (the most affected hearing frequency identified at study entry) in affected ear from baseline to the end of treatment visit (Visit D28± 3).
4. 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 on pure tone

audiometric air conduction testing) in affected ear from baseline to the end of study visit (Visit D84 ± 3)

5. Change in speech discrimination threshold from baseline to
   a. Days 28,
   b. and 84
6. Frequency and severity of tinnitus at Days 7, 14, 28, and 84 assessed by numerical rating scale
   a. severity at Day 28
   b. severity at Day14
   c. severity at Day 7
   d. severity at Day 84

Thus, if significance is not achieved on the higher-ranking endpoint, analysis of lower-ranking endpoints will still be conducted but will be purely exploratory. For example, if significance is not achieved in 2, analysis of 3-6 will still be conducted but will be declared as non-significant and thus purely exploratory. For the Part 1, the high dose will be tested, first, within each secondary endpoint (i.e. 2, 3, 4, 5), then followed by testing the low dose conditionally to the significance of the high dose.

6.13 Pharmacokinetic Analyses

Serum samples will be collected for pharmacokinetic (PK) analysis at pre- and post-dose on Day 14 (V4) and on Day 28 (EoT). Plasma concentration values will be summarized at each relevant timepoint by treatment group using number of non-missing observations, geometric mean, geometric coefficient of variation (CV), defined as $100 * \sqrt{\left(e^{s^2} - 1\right)}$ where s is the SD of the data on a log scale, minimum and maximum.

All PK data will also be listed.

6.14 Safety Analyses

The safety analyses will be presented by the treatment actually received for the Safety analysis set. In the situation of accidental dispensation of two or three distinct treatments to the same patient, the patient will be counted for the whole study on the highest dose received.

6.14.1 Adverse Events

A treatment emergent adverse event (TEAE) is defined as any AE that has an onset on or after the first dose of study drug (without limitation after end of treatment).

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.

Late AE is defined as any AE that has an onset on or later than 3 days after the last study treatment intake.

A treatment-related AE is defined as an AE as being possibly or probably related to the study drug. If an AE has missing or not assessable relationship it is assumed to be related to the study drug for analysis purposes.

Maximum severity will be assumed for an AE with missing severity.

All AEs will be coded using the most recent MedDRA version available at time of database lock. Summaries over system organ class (SOC) and preferred term (PT) by treatment groups, and listings of all TEAEs, Serious Adverse Events (SAEs), AEs leading to withdrawal, and AEs leading to death will be presented. The following tables will be presented for AEs:

- Overall incidence and the number of TEAEs, treatment-related TEAEs, SAEs, TEAEs leading to withdrawal, and TEAEs leading to death.
- TEAE by system organ class and preferred term, incidence and number of events
- Treatment-related TEAE by system organ class and preferred term, incidence and number of events
- Serious TEAE by system organ class and preferred term, incidence and number of events
- Severe TEAE by system organ class and preferred term, incidence and number of events
- TEAE by system organ class, preferred term and maximum severity, incidence
- Treatment-related TEAE by system organ class, preferred term and maximum severity, incidence
- TEAE leading to early withdrawal by system organ class and preferred term, incidence and number of events
- Listing of serious AEs (presented in the Table section of the appendices).
- Listing of AEs leading to withdrawal (presented in the Table section of the appendices)
- Listing of AEs leading to deaths (presented in the Table section of the appendices).

In counting the number of AEs reported, a continuous event (i.e. reported more than once and which did not cease), will be counted only once; non-continuous AE reported several times by the same subject will be counted as multiple events.

A late TEAE is defined as a TEAE that has an onset date 3 days or more after the last intake of study drug.

The outputs listed above will be repeated on the late TEAEs only.

All AEs will be listed (with flags identifying TEAEs and late TEAEs).

SAEs not classified as treatment-emergent will be displayed in a separate listing.

6.14.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each hematology, serum chemistry, and C-reactive protein parameter. For categorical laboratory parameters, subject counts within each category will be summarized. Shift tables from baseline to each post-baseline visit will also be presented, as applicable.

Each measurement (continuous data) will be classified as below, within, or above normal range, based on ranges supplied by the laboratory used. This study utilizes local laboratories only and therefore each local laboratory will provide its reference ranges. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

Moreover, the number and percentage of subjects with treatment-emergent marked laboratory abnormalities will be tabulated for each laboratory parameter for which marked abnormalities are defined in the table below. For a given parameter, percentages will be based on the number of subjects at risk: those not meeting the criterion at baseline (or having a missing baseline value) and having at least one post-baseline value (including post-baseline value after last intake of study drug). The marked laboratory date abnormalities are defined as follows:

Category	Lab Test/ Examination Name	Unit	Marked Abnormalities				
			LL	LLL	HH	HHH	HHHH
CHEMISTRY	Alanine Aminotransferase	U/L			>3ULN	>5ULN	>8ULN
CHEMISTRY	Albumin	g/L	<30	<20			
CHEMISTRY	Alkaline Phosphatase	U/L			>2.5ULN	>5ULN	
CHEMISTRY	Aspartate Aminotransferase	U/L			>3ULN	>5ULN	>8ULN
CHEMISTRY	Bilirubin	umol/L			>2ULN	>5ULN	
CHEMISTRY	Calcium	mmol/L	<2.0	<1.75	>2.9	>3.1	
CHEMISTRY	Creatine Kinase	U/L			>5ULN	>10ULN	
CHEMISTRY	Creatinine	mmol/L			>1.5ULN or (>1.5baseline if baseline > ULN)	>3ULN or (>3baseline if baseline>ULN)	
CHEMISTRY	Creatinine Clearance	mL/min/ 1.73m^2	<60	<30			
CHEMISTRY	Gamma Glutamyl Transferase	U/L			>2.5ULN	>5ULN	
CHEMISTRY	Glucose	mmol/L	<3.0	<2.2	>8.9	>13.9	
CHEMISTRY	Phosphate	mmol/L	<0.8	<0.6			
CHEMISTRY	Potassium	mmol/L	<3.2	<3.0	>5.5	>6.0	
CHEMISTRY	Sodium	mmol/L	<130		>150	>155	
CHEMISTRY	Triglycerides	mmol/L					
CHEMISTRY	Urate	umol/L			>590	>720	
CHEMISTRY	Urea	mmol/L			>2.5ULN	>5ULN	
HEMATOLOGY	Eosinophils	10^9/L			>5.0		
HEMATOLOGY	Hematocrit	Ratio	<0.32(men), <0.28(women)	<0.20	>0.60(men), >0.55 (women)	>0.65	
HEMATOLOGY	Hemoglobin	g/L	<100	<80	>ULN+20 (or >baseline+20 if baseline>ULN)	>ULN+40 (or >baseline+40 if baseline>ULN)	
HEMATOLOGY	Leukocytes	10^9/L	<3.0	<2.0	>20	>100	
HEMATOLOGY	Lymphocytes	10^9/L	<0.8	<0.5	>4.0	>20	
HEMATOLOGY	Neutrophils	10^9/L	<1.5	<1.0			
HEMATOLOGY	Platelets	10^9/L	<75	<50	>600	>999	

A listing of any clinically significant laboratory measurements recorded throughout the study will be presented. For lab parameters that have defined marked abnormalities, the most extreme

abnormality will be listed. All laboratory assessments, including urine and serum pregnancy tests, will also be listed.

6.14.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group and visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Body temperature (degrees Celsius)
- Body weight (kg)

Moreover, the number and percentage of subjects with treatment-emergent marked abnormality will be tabulated for each parameter. Percentages will be based on the number of subjects at risk for the parameter: those having a baseline value and at least one post-baseline value (including post-baseline value after last intake of study drug). The marked vital sign abnormalities are defined as follows:

Parameter	Abnormality
SBP (mmHg)	≤ 95 mmHg and decrease from baseline ≥ 20 mmHg, ≥ 160 mmHg and increase from baseline ≥ 20 mmHg
DBP (mmHg)	≤ 45 mmHg and decrease from baseline ≥ 10 mmHg, ≥ 110 mmHg and increase from baseline ≥ 10 mmHg
HR (bpm)	≤ 50 bpm and decrease from baseline ≥ 20 bpm, ≥ 120 bpm and increase from baseline ≥ 20 bpm

6.14.4 Physical Examination

The body systems within the physical examination data will be summarized by treatment and visit. In addition, shift tables in terms of findings (Normal, Abnormal NCS, Abnormal CS) from baseline to Day 28 (EoT) and Day 84 (EoS/Follow-up) for each body system will be presented. Details of clinically significant findings will be listed.

6.14.5 Otoscopy

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. Findings (Normal, Abnormal NCS and Abnormal CS) will be summarized for each ear by

treatment group and visit. In addition, shift tables from baseline to all post-baseline visits will be presented for each ear by treatment group.

All otoscopy data will be listed.

6.14.6 Tympanometry

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.

Findings (Normal, Abnormal NCS, Abnormal CS) will be summarized for each ear by treatment group and visit. Shift tables from baseline to each post-baseline visit will be presented for each ear by treatment group.

All tympanometry data will be listed.

6.14.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

C-SSRS will be used to assess suicidal ideations and behaviors. Number of subjects that responded 'yes' to any of the C-SSRS Suicidal Ideation Items, as described in Section 6.2.12, will be presented by treatment group, and will be tabulated separately for baseline and post-baseline assessments. Similarly, number of subjects that responded 'yes' to any of the C-SSRS Suicidal Behavioral Items, as described in Section 6.2.12, will be presented by treatment group, and will be tabulated separately at baseline and post-baseline assessments.

Derived C-SSRS data as described in Section 6.2.12 will be listed for baseline and post-baseline assessments for all subjects.

7 INTERIM ANALYSIS

Protocol version 4.0 introduced two interim GST looks to 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 Hwang-Shih-DeCani alpha spending function) and a binding futility procedure (with a gamma function of parameter -4 as Hwang-Shih-DeCani beta spending function). At each GST look, the z-score statistic was to be calculated for the estimated difference of high dose versus placebo. The GST looks were 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 were planned when 63, 85 and 111 patients, respectively (when 41, 55, 74 patients could 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 were to be used without any change.

Further details of the GST analyses are described in a separate SAP. The GST analyses were to be undertaken by a separate statistical group contracted by the sponsor.

The first GST look was performed, and the outcome was a recommendation to continue Part 1 in the absence of crossing of any boundary. The second GST look was not performed because all amendment protocol approvals were not obtained yet at time when the sample size of the second GST was reached. The final look will finally not be performed as it does not have enough added value compared to the analysis planned in the DMC SAP section 2.6 (same boundary p-value of 0.0500 one-sided for both analyses).

8 CHANGES TO PLANNED PROTOCOL ANALYSIS

1. Clarified the primary efficacy endpoint, that is, added “on pure tone audiometric air conduction testing” since there are two PTAs – bone and air conduction. Inclusion criteria #3.1-3.2 of the protocol implies the primary efficacy endpoint is based on the pure tone audiometric air conduction testing only and that the audiometric bone conduction testing is useful only at study entry to check the exclusion criterion #14. Moreover, the definition of hearing loss in in Section 10.1.1 of the protocol indicated the use of air pure tone average.

2. Clarified the secondary efficacy endpoint "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)", that is, "frequencies" was changed to "frequency" since the endpoint pertains only to a single most affected frequency.
3. Added "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 on pure tone audiometric air conduction testing) in affected ear from baseline to the end of study visit (Visit D84 ± 3)" as a secondary endpoint to cover the first secondary objective "To confirm the maintenance of any early efficacy on hearing loss at 12-week".
4. Removed the exploratory efficacy endpoint "Change in PTA from baseline to Day 7, Day 14 and end of study visit (Visit D84±3)" since this is already covered by the added secondary efficacy endpoint (see above item).
5. Multiplicity adjustment for Part 1 and Part 2 of the study was specified.
6. The combined analysis of all primary endpoint data from Part 1 and Part 2 in a meta-analysis was not further detailed and finally removed.
7. The first-order autoregressive covariance structure was added as an additional possible choice in case of absence of convergence of the unstructured covariance in the model for repeated measurements.
8. The second GST look was not performed because all amendment protocol approvals were not obtained yet at time when the sample size of the second GST was reached. The final look will finally not be performed as it does not have enough added value compared to the analysis planned in the DMC SAP section 2.6 (same boundary p-value of 0.0500 one-sided for both analyses).
9. Definition of treatment-emergent adverse events was modified to have no limitation in time after the last dose intake of study drug (instead of excluding events occurring later than five half-lives after the last lost dose). Late TEAEs were defined as TEAEs with onset date on 3 days or more after the last study drug intake.
10. Number and percentage of subjects with treatment-emergent abnormality was added in the analysis of laboratory data and vital signs.

9 REFERENCES

1. Staecker et al., Efficacy and Safety of AM-111 in the Treatment of Acute Unilateral Sudden Deafness-A Double-blind, Randomized, Placebo-controlled Phase 3 Study, Otol Neurotol 2019;40(5):584-594.
2. Suckfuell et al., Efficacy and safety of AM-111 in the treatment of acute sensorineural hearing loss: a double-blind, randomized, placebo-controlled phase II study, Otol Neurotol 2014;35(8):1317-26.
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4. Marcus R; Peritz E; Gabriel KR, On closed testing procedures with special reference to ordered analysis of variance, Biometrika. 1976; 63: 655–660.
5. Koch GG, Gansky SASA, Statistical Considerations for Multiplicity in Confirmatory Protocols, Drug Information Journal 1996, Vol. 30. pp. 523-534.
6. Carpenter JR, Roger JH, Kenward MG., Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat. 2013;23(6):1352–71.
7. Rubin DB. Multiple imputation for nonresponse in surveys. New York, NY, USA: John Wiley & Sons; 1987.

10 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of numbers and manual review of format (IP)
- Independent programming by statistician of numbers and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Furthermore, separate set of outputs will be produced for the Part 1 and Part 2 of the study:

10.1 Part 1 outputs

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1a	Subject Disposition Part 1 – All Screened Subjects	IP	
14.1.1.2a	Analysis Sets Part 1 – All Randomized Subjects	IP	
14.1.1.3.1a	Protocol Deviations Part 1 – Intent-to-Treat Analysis Set	IP	
14.1.1.3.2a	COVID-19-related Protocol Deviations Part 1 – Intent-to-Treat Analysis Set	IP	14.1.1.3.1a
14.1.1.4a	Stratification factors Part 1 – Intent-to-Treat Analysis Set	IP	
14.1.1.5a	Possible Discrepancies in Stratification Factors Data Part 1 – Intent-to-Treat Analysis Set	IP	
14.1.2	**Demographics**		
14.1.2.1a	Demographics Part 1 – Intent-to-Treat Analysis Set	IP	
14.1.3	**Baseline Characteristics**		
14.1.3.1a	Medical and Surgical History Prior to Screening Part 1 – Intent-to-Treat Analysis Set	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.1.3.2a	Medical and Surgical History Ongoing at Screening Part 1– Intent-to-Treat Analysis Set	IP	14.1.3.1a
14.1.3.3a	Hearing Loss - Current Episode at Time of Randomization Part 1 – Intent-to-Treat Analysis Set	IP	
14.1.3.4a	Otologic History Part 1 – Intent-to-Treat Analysis Set	IP	
14.1.3.5a	Air Conduction PTA at Baseline Part 1 – Intent-to-Treat Analysis Set	IP	
14.1.3.6a	Other Relevant Baseline Characteristics Part 1 – Intent-to-Treat Analysis Set	IP	
14.2	**Efficacy Data**		
14.2.1	**Primary Efficacy Endpoint**		
14.2.1.1a	Primary Analysis: MMRM of Change in Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Treatment Part 1 – Intent-to-Treat Analysis Set	Stat IP	
14.2.1.2a	Sensitivity Analysis: MMRM of Change in Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Treatment Part 1 – Per-Protocol Analysis Set	Stat IP	14.2.1.1a
14.2.1.3a	Sensitivity Analysis: ANCOVA of Change in Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Treatment (MNAR: Copy Reference Imputation) Part 1 – Intent-to-Treat Analysis Set	Stat IP	
14.2.1.4a	Sensitivity Analysis: MMRM of Change in Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Treatment (Assessments after rescue therapy set to missing and each Day 28 assessment after rescue therapy imputed by subject baseline) Part 1 – Intent-to-Treat Analysis Set	Stat IP	14.2.1.1a

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.2.1.5a	Summary of Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Treatment – Descriptive Statistics Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.2	**Secondary Efficacy Endpoints**		
14.2.2.1.1a	MMRM of Change in Pure Tone Audiometry (2 Most Affected Frequencies) in Affected Ear from Baseline to the End of Treatment Part 1 – Intent-to-Treat Analysis Set	Stat IP	14.2.1.1a
14.2.2.1.2a	MMRM of Change in Pure Tone Audiometry (2 Most Affected Frequencies) in Affected Ear from Baseline to the End of Treatment Part 1 – Per-Protocol Analysis Set	Stat IP	14.2.1.1a
14.2.2.2.1a	MMRM of Change in Pure Tone Audiometry (Most Affected Frequency) in Affected Ear from Baseline to the End of Treatment Part 1 – Intent-to-Treat Analysis Set	Stat IP	14.2.1.1a
14.2.2.2.2a	MMRM of Change in Pure Tone Audiometry (Most Affected Frequency) in Affected Ear from Baseline to the End of Treatment Part 1 – Per-Protocol Analysis Set	Stat IP	14.2.1.1a
14.2.2.3a	MMRM of Change in Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Study Part 1 – Intent-to-Treat Analysis Set	Stat IP	
14.2.2.4a	MMRM of Change in Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Study Part 1 – Per-Protocol Analysis Set	Stat IP	14.2.2.3a
14.2.2.4.1a	MMRM of Change in Speech Discrimination Threshold from Baseline to Post-baseline Visits Part 1 – Intent-to-Treat Analysis Set	Stat IP	14.2.2.3a
14.2.2.4.2a	MMRM of Change in Speech Discrimination Threshold from Baseline to Post-baseline Visits Part 1 – Per-Protocol Analysis Set	Stat IP	14.2.2.3a

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.2.2.5.1a	MMRM of Change in Severity of Tinnitus (Numerical Rating Scale) from Baseline to Post-baseline Visits Part 1 – Intent-to-Treat Analysis Set	Stat IP	14.2.2.3a
14.2.2.5.2a	MMRM of Change in Severity of Tinnitus (Numerical Rating Scale) from Baseline to Post-baseline Visits Part 1 – Per-Protocol Analysis Set	Stat IP	14.2.2.3a
14.2.2.5.3a	Frequency and Severity of Tinnitus (Numerical Rating Scale) at Day 7, 14, 28 and 84 Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.2.5.4a	Frequency and Severity of Tinnitus (Numerical Rating Scale) at Day 7, 14, 28 and 84 Part 1 – Per-Protocol Analysis Set	IP	14.2.2.5.3a
14.2.3	**Exploratory Endpoints**		
14.2.3.1a	Proportion of Patients with Complete Hearing Recovery or Hearing Similar to Unaffected Contralateral Ear Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.2a	Proportion of Patients with Marked Improvement Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.3a	Proportion of Patients with Air Pure Tone Audiometry Threshold of >35dB and >90dB on Day 7, Day 14, and End of Study Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.4a	Proportion of Responders (Improvement of 10 dB or more) in Pure Tone Audiometry Threshold Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.5a	Word Recognition Score at 80 dB and 60 dB in the Affected Ear Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.6a	Time of Onset of Symptoms to First Study Drug Intake Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.7a	Frequency and Severity of any Vertigo at Day 1, 7, 14, 28 and 84 Part 1 – Intent-to-Treat Analysis Set	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.2.3.8a	Tinnitus Burden Based on the Change in Tinnitus QoL Scores at Day 1, 7, 14, 28 and 84 Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.9a	Change in Biomarkers from Baseline to Post-baseline Visits Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.10.1a	Summary of EQ-5D-5L Responses at Baseline and Post-baseline Visits Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.10.2a	EQ-5D-5L Responses, Shifts from Baseline to Day 28 and 84 Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.10.3a	Summary of EQ-5D-5L Dichotomized Responses at Baseline and Post-baseline Visits Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.10.4a	Change in EQ Visual Analogue Scale from Baseline to Day 28 and 84 Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.11a	Change in DPOAE at Days 7, 14, 28, and 84 Compared to Baseline Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.3.12a	Change in TEOAE at Days 7, 14, 28 and 84 Compared to Baseline Part 1 – Intent-to-Treat Analysis Set	IP	
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1.1a	Overall Summary of Treatment-Emergent Adverse Events (TEAEs) Part 1 – Safety Analysis Set	IP	
14.3.1.1.2a	Overall Summary of Late Adverse Events Part 1 – Safety Analysis Set	IP	
14.3.1.2.1a	TEAEs by Primary System Organ Class and Preferred Term Part 1 – Safety Analysis Set	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.2.2a	Late AEs by Primary System Organ Class and Preferred Term Part 1 – Safety Analysis Set	IP	14.3.1.2.1a
14.3.1.3.1a	Treatment-Related TEAEs by Primary System Organ Class and Preferred Term Part 1 – Safety Analysis Set	IP	14.3.1.2.1a
14.3.1.3.2a	Treatment-Related Late AEs by Primary System Organ Class and Preferred Term Part 1 – Safety Analysis Set	IP	14.3.1.2.1a
14.3.1.4.1a	Serious TEAEs by Primary System Organ Class and Preferred Term Part 1 – Safety Analysis Set	IP	14.3.1.2.1a
14.3.1.4.2a	Serious Late AEs by Primary System Organ Class and Preferred Term Part 1 – Safety Analysis Set	IP	14.3.1.2.1a
14.3.1.5.1a	Severe TEAEs by Primary System Organ Class and Preferred Term Part 1 – Safety Analysis Set	IP	14.3.1.2.1a
14.3.1.5.2a	Severe Late AEs by Primary System Organ Class and Preferred Term Part 1 – Safety Analysis Set	IP	14.3.1.2.1a
14.3.1.6.1a	TEAEs by Primary System Organ Class Preferred Term, and Severity Part 1 – Safety Analysis Set	IP	
14.3.1.6.2a	Late AEs by Primary System Organ Class Preferred Term, and Severity Part 1 – Safety Analysis Set	IP	14.3.1.6.1a
14.3.1.7.1a	Treatment-Related TEAEs by Primary System Organ Class, Preferred Term, and Severity Part 1 – Safety Analysis Set	IP	14.3.1.6.1a
14.3.1.7.2a	Treatment-Related Late AEs by Primary System Organ Class, Preferred Term, and Severity Part 1 – Safety Analysis Set	IP	14.3.1.6.1a
14.3.1.8.1a	TEAEs Leading to Early Withdrawal by Primary System Organ Class and Preferred Term Part 1 – Safety Analysis Set	IP	14.3.1.2.1a

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.8.2a	Late AEs Leading to Early Withdrawal by Primary System Organ Class and Preferred Term Part 1 – Safety Analysis Set	IP	14.3.1.2.1a
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.2.1a	Listing of Serious Adverse Events Part 1 – Safety Analysis Set	IP	
14.3.2.2a	Listing of Adverse Events Leading to Early Withdrawal Part 1 – Safety Analysis Set	IP	
14.3.2.3a	Listing of Adverse Events Leading to Deaths Part 1 – Safety Analysis Set	IP	
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		
14.3.4	**Abnormal Laboratory Values**		
14.3.4.1a	Listing of Clinically Significant Laboratory Values Part 1 – Safety Analysis Set	IP	
14.3.5	**Extent of Exposure, Dosage Information, and Compliance**		
14.3.5.1a	Extent of Exposure to Study Drug Part 1 – Safety Analysis Set	IP	
14.3.5.2a	Treatment Compliance Part 1 – Safety Analysis Set	IP	
14.3.6	**Vital Signs and Physical Examination**		
14.3.6.1a	Vital Signs, Descriptive Statistics and Changes from Baseline to Post-baseline Assessments Part 1 – Safety Analysis Set	IP	
14.3.6.2a	Vital Signs, Treatment-Emergent Marked Abnormalities Part 1 – Safety Analysis Set	IP	
14.3.6.3a	Physical Examination, Descriptive Statistics of Post-baseline Assessments Part 1 – Safety Analysis Set	IP	
14.3.6.4a	Physical Examination, Shifts from Baseline to Post-baseline Assessments Part 1 – Safety Analysis Set	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.7	**Other Safety**		
14.3.7.1a	Hematology, Change from Baseline to Post-baseline Assessments Part 1 – Safety Analysis Set	IP	
14.3.7.2a	Hematology, Normal Range Shifts Part 1 – Safety Analysis Set	IP	
14.3.7.3a	Hematology, Treatment-Emergent Marked Abnormalities	IP	
14.3.7.4a	Serum Chemistry, Change from Baseline to Post-baseline Assessments Part 1 – Safety Analysis Set	IP	14.3.7.1a
14.3.7.5a	Serum Chemistry, Normal Range Shifts Part 1 – Safety Analysis Set	IP	14.3.7.2a
14.3.7.6a	Serum Chemistry, Treatment-Emergent Marked Abnormalities	IP	
14.3.7.7a	Otoscopy, Descriptive Statistics Part 1 – Safety Analysis Set	IP	14.3.6.2a
14.3.7.8a	Otoscopy, Shift from Baseline to Post-baseline Assessments, Findings Part 1 – Safety Analysis Set	IP	14.3.6.3a
14.3.7.9a	Tympanometry, Descriptive Statistics Part 1 – Safety Analysis Set	IP	14.3.6.2a
14.3.7.10a	Tympanometry, Shift from Baseline to Post-baseline Assessments, Findings Part 1 – Safety Analysis Set	IP	14.3.6.3a
14.3.7.11.1a	Number and Percentage of Subjects with a Response of Yes to Any Columbia Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation Item at Baseline Part 1 – Safety Analysis Set	IP	
14.3.7.11.2a	Number and Percentage of Subjects with a Response of Yes to Any Columbia Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation Item at Any Time Post-baseline Part 1 – Safety Analysis Set	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.7.11.3a	Number and Percentage of Subjects with a Response of Yes to Any Columbia Suicide Severity Rating Scale (C-SSRS) Suicidal Behavioral Item at Baseline Part 1 – Safety Analysis Set	IP	
14.3.7.11.4a	Number and Percentage of Subjects with a Response of Yes to Any Columbia Suicide Severity Rating Scale (C-SSRS) Suicidal Behavioral Item at Any Time Post-baseline Part 1 – Safety Analysis Set	IP	
14.3.8	**Concomitant Medication**		
14.3.8.1a	Prior Medication Part 1 – Safety Analysis Set	IP	
14.3.8.2a	Concomitant Medication Part 1 – Safety Analysis Set	IP	14.3.8.1a
14.3.8.3a	Study Treatment Concomitant Medication Part 1 – Safety Analysis Set	IP	14.3.8.1a
14.3.8.4a	Prior Oral Corticosteroids Part 1 – Safety Analysis Set	IP	14.3.8.1a
14.3.8.5a	Concomitant Oral Corticosteroids Part 1 – Safety Analysis Set	IP	14.3.8.1a
14.3.8.6a	Corticosteroids as Rescue Treatment Part 1 – Safety Analysis Set	IP	
14.4	**PK Tables**		
14.4.1a	Serum Concentration, Descriptive Statistics Part 1 – Safety Analysis Set	IP	
14.6	**Other Data**		

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.2.1.1a	Line plot of Change in Pure Tone Audiometry (3 most affected frequencies) in the Affected Ear Over Time Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.1.2a	Line plot of Change in Pure Tone Audiometry (2 most affected frequencies) in the Affected Ear Over Time Part 1 – Intent-to-Treat Analysis Set	IP	14.2.1.1a
14.2.1.3a	Line plot of Change in Pure Tone Audiometry (most affected frequency) in the Affected Ear Over Time Part 1 – Intent-to-Treat Analysis Set	IP	14.2.1.1a
14.2.1.4a	Line plot of Change in Speech Recognition Threshold Over Time Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.1.5a	Line Plot of Speech Discrimination Threshold Over Time Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.1.6a	Bar Chart of the Frequency of Tinnitus at Each Timepoint Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.1.7a	Proportion of Responders (Improvement of 10 dB or more) in Pure Tone Audiometry Threshold Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.1.8.1a	Percent Change in Word Recognition Score at 80 dB and 60 dB in the Affected Ear Over Time Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.1.8.2a	Word Recognition Score at 80 and 60 dB in the Affected Ear Over Time Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.1.8.3a	Absolute Difference in Word Recognition Score between the Affected and Reference Ear at 80 and 60 dB Over Time Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.1.9a	Relationship of Time of Onset of Symptoms to First Study Drug Intake and the Primary Endpoint Part 1 – Intent-to-Treat Analysis Set	IP	
14.2.1.10a	Bar Chart of the Frequency of Vertigo at Each Timepoint Part 1 – Intent-to-Treat Analysis Set	IP	14.2.1.6a

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1a	Screen Failures Part 1 – All Screened Subjects	IP	
16.2.1.2a	Early Withdrawals Part 1 – All Randomized Subjects	IP	
16.2.1.3a	Inclusion and Exclusion Criteria – Screen Failures Part 1 – All Screened Subjects	IP	
16.2.2	**Protocol Deviations**		
16.2.2.1a	Protocol Deviations Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.3	**Subjects Excluded from the Efficacy Analyses**		
16.2.3.1a	Analysis Sets Part 1 – All Randomized Subjects	IP	
16.2.4	**Demographic Data**		
16.2.4.1a	Demographics Data Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.4.2a	Baseline Characteristics and Other Relevant Data Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.4.3a	Medical History Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.4.4a	Otologic History Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.4.5a	Ear, Neck, Nose and Throat Problems Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.4.6a	Baseline Pure Tone Audiometry Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.4.7a	Raw Data on Pure Tone Audiometry Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.5	**Compliance and/or Drug Concentration Data**		
16.2.5.1a	Prior, Study Concomitant and Study Treatment Concomitant Medications Part 1 – Safety Analysis Set	IP	
16.2.5.2a	Prior and Concomitant Oral Corticosteroids	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
	Part 1 – Safety Analysis Set		
16.2.5.3a	Study Treatment Exposure Part 1 – Safety Analysis Set	IP	
16.2.5.4a	PK Sample Collection Data Part 1 – Pharmacokinetic Analysis Set	IP	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1a	PTA Data Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.6.2a	Speech Discrimination Threshold Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.6.3a	Vertigo Data Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.6.4a	Tinnitus Severity Data Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.6.5a	Tinnitus Questionnaire Data Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.6.6a	DPOAE Data Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.6.7a	TEOAE Data Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.6.8a	EQ-5D-5L Data Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.6.9a	Word Recognition Data Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.6.10a	Biomarkers Data Part 1 – Intent-to-Treat Analysis Set	IP	
16.2.7	**Adverse Event Listings**		
16.2.7.1a	Adverse Events Part 1 – Safety Analysis Set	IP	
16.2.7.2a	Late Adverse Events Part 1 – Safety Analysis Set		
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1a	Hematology Data Part 1 – Safety Analysis Set	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.8.2a	Serum Chemistry Data Part 1 – Safety Analysis Set	IP	
16.2.8.3a	C-Reactive Protein Data Part 1 – Safety Analysis Set	IP	
16.2.8.4a	Pregnancy Test Data Part 1 – Safety Analysis Set	IP	
16.2.8.5a	Physical Examination Data Part 1 – Safety Analysis Set	IP	
16.2.8.6a	Vital Signs Data Part 1 – Safety Analysis Set	IP	
16.2.8.7a	Otoscopy Data Part 1 – Safety Analysis Set	IP	
16.2.8.8a	Tympanometry Data Part 1 – Safety Analysis Set	IP	
16.2.8.9a	Suicidality Assessment (C-SSRS) Part 1 – Safety Analysis Set	IP	

10.2 Part 2 outputs

Part 2 outputs the same as for Part 1 but for 2 treatment arms.

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1b	Subject Disposition Part 2 – All Screened Subjects	IP	
14.1.1.2b	Analysis Sets Part 2 – All Randomized Subjects	IP	
14.1.1.3.1b	Protocol Deviations Part 2 – Intent-to-Treat Analysis Set	IP	
14.1.1.3.2b	COVID-19-related Protocol Deviations Part 2 – Intent-to-Treat Analysis Set	IP	14.1.1.3.1b
14.1.1.4b	Stratification factors Part 2 – Intent-to-Treat Analysis Set	IP	
14.1.1.5b	Possible Discrepancies in Stratification Factors Data Part 2 – Intent-to-Treat Analysis Set	IP	
14.1.2	**Demographics**		
14.1.2.1b	Demographics Part 2 – Intent-to-Treat Analysis Set	IP	
14.1.3	**Baseline Characteristics**		
14.1.3.1b	Medical and Surgical History Prior to Screening Part 2 – Intent-to-Treat Analysis Set	IP	
14.1.3.2b	Medical and Surgical History Ongoing at Screening Part 2– Intent-to-Treat Analysis Set	IP	14.1.3.1b
14.1.3.3b	Hearing Loss - Current Episode at Time of Randomization Part 2 – Intent-to-Treat Analysis Set	IP	
14.1.3.4b	Otologic History Part 2 – Intent-to-Treat Analysis Set	IP	
14.1.3.5b	Air Conduction PTA at Baseline Part 2 – Intent-to-Treat Analysis Set	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.1.3.6b	Other Relevant Baseline Characteristics Part 2 – Intent-to-Treat Analysis Set	IP	
14.2	**Efficacy Data**		
14.2.1	**Primary Efficacy Endpoint**		
14.2.1.1b	Primary Analysis: MMRM of Change in Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Treatment Part 2 – Intent-to-Treat Analysis Set	Stat IP	
14.2.1.2b	Sensitivity Analysis: MMRM of Change in Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Treatment Part 2 – Per-Protocol Analysis Set	Stat IP	14.2.1.1b
14.2.1.3b	Sensitivity Analysis: ANCOVA of Change in Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Treatment (MNAR: Copy Reference Imputation) Part 2 – Intent-to-Treat Analysis Set	Stat IP	
14.2.1.4b	Sensitivity Analysis: MMRM of Change in Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Treatment (Assessments after rescue therapy set to missing and each Day 28 assessment after rescue therapy imputed by subject baseline) Part 2 – Intent-to-Treat Analysis Set	Stat IP	14.2.1.1b
14.2.1.5b	Summary of Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Treatment – Descriptive Statistics Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.2	**Secondary Efficacy Endpoints**		
14.2.2.1.1 b	MMRM of Change in Pure Tone Audiometry (2 Most Affected Frequencies) in Affected Ear from Baseline to the End of Treatment	Stat IP	14.2.1.1b

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	Part 2 – Intent-to-Treat Analysis Set		
14.2.2.1.2b	MMRM of Change in Pure Tone Audiometry (2 Most Affected Frequencies) in Affected Ear from Baseline to the End of Treatment Part 2 – Per-Protocol Analysis Set	Stat IP	14.2.1.1b
14.2.2.2.1b	MMRM of Change in Pure Tone Audiometry (Most Affected Frequency) in Affected Ear from Baseline to the End of Treatment Part 2 – Intent-to-Treat Analysis Set	Stat IP	14.2.1.1b
14.2.2.2.2b	MMRM of Change in Pure Tone Audiometry (Most Affected Frequency) in Affected Ear from Baseline to the End of Treatment Part 2 – Per-Protocol Analysis Set	Stat IP	14.2.1.1b
14.2.2.3b	MMRM of Change in Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Study Part 2 – Intent-to-Treat Analysis Set	Stat IP	
14.2.2.4b	MMRM of Change in Pure Tone Audiometry (3 contiguous most affected hearing frequencies) in the Affected Ear from Baseline to the End of Study Part 2 – Per-Protocol Analysis Set	Stat IP	14.2.2.3b
14.2.2.4.1b	MMRM of Change in Speech Discrimination Threshold from Baseline to Post-baseline Visits Part 2 – Intent-to-Treat Analysis Set	Stat IP	14.2.2.3b
14.2.2.4.2b	MMRM of Change in Speech Discrimination Threshold from Baseline to Post-baseline Visits Part 2 – Per-Protocol Analysis Set	Stat IP	14.2.2.3b
14.2.2.5.1b	MMRM of Change in Severity of Tinnitus (Numerical Rating Scale) from Baseline to Post-baseline Visits Part 2 – Intent-to-Treat Analysis Set	Stat IP	14.2.2.3b
14.2.2.5.2b	MMRM of Change in Severity of Tinnitus (Numerical Rating Scale) from Baseline to Post-baseline Visits Part 2 – Per-Protocol Analysis Set	Stat IP	14.2.2.3b
14.2.2.5.3b	Frequency and Severity of Tinnitus (Numerical Rating Scale) at Day 7, 14, 28 and 84 Part 2 – Intent-to-Treat Analysis Set	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.2.2.5.4 b	Frequency and Severity of Tinnitus (Numerical Rating Scale) at Day 7, 14, 28 and 84 Part 2 – Per-Protocol Analysis Set	IP	14.2.2.5.3b
14.2.3	**Exploratory Endpoints**		
14.2.3.1b	Proportion of Patients with Complete Hearing Recovery or Hearing Similar to Unaffected Contralateral Ear Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.2b	Proportion of Patients with Marked Improvement Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.3b	Proportion of Patients with Air Pure Tone Audiometry Threshold of >35dB and >90dB on Day 7, Day 14, and End of Study Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.4b	Proportion of Responders (Improvement of 10 dB or more) in Pure Tone Audiometry Threshold Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.5b	Word Recognition Score at 80 dB and 60 dB in the Affected Ear Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.6b	Time of Onset of Symptoms to First Study Drug Intake Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.7b	Frequency and Severity of any Vertigo at Day 1, 7, 14, 28 and 84 Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.8b	Tinnitus Burden Based on the Change in Tinnitus QoL Scores at Day 1, 7, 14, 28 and 84 Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.9b	Change in Biomarkers from Baseline to Post-baseline Visits Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.10. 1b	Summary of EQ-5D-5L Responses at Baseline and Post-baseline Visits Part 2 – Intent-to-Treat Analysis Set	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.2.3.10.2b	EQ-5D-5L Responses, Shifts from Baseline to Day 28 and 84 Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.10.3b	Summary of EQ-5D-5L Dichotomized Responses at Baseline and Post-baseline Visits Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.10.4b	Change in EQ Visual Analogue Scale from Baseline to Day 28 and 84 Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.11b	Change in DPOAE at Days 7, 14, 28, and 84 Compared to Baseline Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.3.12b	Change in TEOAE at Days 7, 14, 28 and 84 Compared to Baseline Part 2 – Intent-to-Treat Analysis Set	IP	
14.3	**Safety Data**		
14.3.1	**Displays of Adverse Events**		
14.3.1.1.1b	Overall Summary of Treatment-Emergent Adverse Events (TEAEs) Part 2 – Safety Analysis Set	IP	
14.3.1.1.2b	Overall Summary of Late Adverse Events Part 2 – Safety Analysis Set	IP	
14.3.1.2.1b	TEAEs by Primary System Organ Class and Preferred Term Part 2 – Safety Analysis Set	IP	
14.3.1.2.2b	Late AEs by Primary System Organ Class and Preferred Term Part 2 – Safety Analysis Set	IP	14.3.1.2.1b
14.3.1.3.1b	Treatment-Related TEAEs by Primary System Organ Class and Preferred Term Part 2 – Safety Analysis Set	IP	14.3.1.2.1b
14.3.1.3.2b	Treatment-Related Late AEs by Primary System Organ Class and Preferred Term Part 2 – Safety Analysis Set	IP	14.3.1.2.1b

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.4.1b	Serious TEAEs by Primary System Organ Class and Preferred Term Part 2 – Safety Analysis Set	IP	14.3.1.2.1b
14.3.1.4.2b	Serious Late AEs by Primary System Organ Class and Preferred Term Part 2 – Safety Analysis Set	IP	14.3.1.2.1b
14.3.1.5.1b	Severe TEAEs by Primary System Organ Class and Preferred Term Part 2 – Safety Analysis Set	IP	14.3.1.2.1b
14.3.1.5.2b	Severe Late AEs by Primary System Organ Class and Preferred Term Part 2 – Safety Analysis Set	IP	14.3.1.2.1b
14.3.1.6.1b	TEAEs by Primary System Organ Class Preferred Term, and Severity Part 2 – Safety Analysis Set	IP	
14.3.1.6.2b	Late AEs by Primary System Organ Class Preferred Term, and Severity Part 2 – Safety Analysis Set	IP	14.3.1.6.1b
14.3.1.7.1b	Treatment-Related TEAEs by Primary System Organ Class, Preferred Term, and Severity Part 2 – Safety Analysis Set	IP	14.3.1.6.1b
14.3.1.7.2b	Treatment-Related Late AEs by Primary System Organ Class, Preferred Term, and Severity Part 2 – Safety Analysis Set	IP	14.3.1.6.1b
14.3.1.8.1b	TEAEs Leading to Early Withdrawal by Primary System Organ Class and Preferred Term Part 2 – Safety Analysis Set	IP	14.3.1.2.1b
14.3.1.8.2b	Late AEs Leading to Early Withdrawal by Primary System Organ Class and Preferred Term Part 2 – Safety Analysis Set	IP	14.3.1.2.1b
14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
14.3.2.1b	Listing of Serious Adverse Events Part 2 – Safety Analysis Set	IP	
14.3.2.2b	Listing of Adverse Events Leading to Early Withdrawal	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
	Part 2 – Safety Analysis Set		
14.3.2.3b	Listing of Adverse Events Leading to Deaths Part 2 – Safety Analysis Set	IP	
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events**		
14.3.4	**Abnormal Laboratory Values**		
14.3.4.1b	Listing of Clinically Significant Laboratory Values Part 2 – Safety Analysis Set	IP	
14.3.5	**Extent of Exposure, Dosage Information, and Compliance**		
14.3.5.1b	Extent of Exposure to Study Drug Part 2 – Safety Analysis Set	IP	
14.3.5.2b	Treatment Compliance Part 2 – Safety Analysis Set	IP	
14.3.6	**Vital Signs and Physical Examination**		
14.3.6.1b	Vital Signs, Descriptive Statistics and Changes from Baseline to Post-baseline Assessments Part 2 – Safety Analysis Set	IP	
14.3.6.2b	Vital Signs, Treatment-Emergent Marked Abnormalities Part 2 – Safety Analysis Set	IP	
14.3.6.3b	Physical Examination, Descriptive Statistics of Post-baseline Assessments Part 2 – Safety Analysis Set	IP	
14.3.6.4b	Physical Examination, Shifts from Baseline to Post-baseline Assessments Part 2 – Safety Analysis Set	IP	
14.3.7	**Other Safety**		
14.3.7.1b	Hematology, Change from Baseline to Post-baseline Assessments Part 2 – Safety Analysis Set	IP	
14.3.7.2b	Hematology, Normal Range Shifts Part 2 – Safety Analysis Set	IP	
14.3.7.3b	Hematology, Treatment-Emergent Marked Abnormalities	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.7.4b	Serum Chemistry, Change from Baseline to Post-baseline Assessments Part 2 – Safety Analysis Set	IP	14.3.7.1b
14.3.7.5b	Serum Chemistry, Normal Range Shifts Part 2 – Safety Analysis Set	IP	14.3.7.2b
14.3.7.6b	Serum Chemistry, Treatment-Emergent Marked Abnormalities	IP	
14.3.7.7b	Otoscopy, Descriptive Statistics Part 2 – Safety Analysis Set	IP	14.3.6.2b
14.3.7.8b	Otoscopy, Shift from Baseline to Post-baseline Assessments, Findings Part 2 – Safety Analysis Set	IP	14.3.6.3b
14.3.7.9b	Tympanometry, Descriptive Statistics Part 2 – Safety Analysis Set	IP	14.3.6.2b
14.3.7.10b	Tympanometry, Shift from Baseline to Post-baseline Assessments, Findings Part 2 – Safety Analysis Set	IP	14.3.6.3b
14.3.7.11.1b	Number and Percentage of Subjects with a Response of Yes to Any Columbia Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation Item at Baseline Part 2 – Safety Analysis Set	IP	
14.3.7.11.2b	Number and Percentage of Subjects with a Response of Yes to Any Columbia Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation Item at Any Time Post-baseline Part 2 – Safety Analysis Set	IP	
14.3.7.11.3b	Number and Percentage of Subjects with a Response of Yes to Any Columbia Suicide Severity Rating Scale (C-SSRS) Suicidal Behavioral Item at Baseline Part 2 – Safety Analysis Set	IP	
14.3.7.11.4b	Number and Percentage of Subjects with a Response of Yes to Any Columbia Suicide Severity Rating Scale (C-SSRS) Suicidal Behavioral Item at Any Time Post-baseline Part 2 – Safety Analysis Set	IP	
14.3.8	**Concomitant Medication**		

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.8.1b	Prior Medication Part 2 – Safety Analysis Set	IP	
14.3.8.2b	Concomitant Medication Part 2 – Safety Analysis Set	IP	14.3.8.1b
14.3.8.3b	Study Treatment Concomitant Medication Part 2 – Safety Analysis Set	IP	14.3.8.1b
14.3.8.4b	Prior Oral Corticosteroids Part 2 – Safety Analysis Set	IP	14.3.8.1b
14.3.8.5b	Concomitant Oral Corticosteroids Part 2 – Safety Analysis Set	IP	14.3.8.1b
14.3.8.6b	Corticosteroids as Rescue Treatment Part 2 – Safety Analysis Set	IP	
14.4	**PK Tables**		
14.4.1b	Serum Concentration, Descriptive Statistics Part 2 – Safety Analysis Set	IP	
14.6	**Other Data**		

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.2.1.1b	Line plot of Change in Pure Tone Audiometry (3 most affected frequencies) in the Affected Ear Over Time Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.1.2b	Line plot of Change in Pure Tone Audiometry (2 most affected frequencies) in the Affected Ear Over Time Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.1.3b	Line plot of Change in Pure Tone Audiometry (most affected frequency) in the Affected Ear Over Time Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.1.4b	Line plot of Change in Speech Recognition Threshold Over Time Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.1.5b	Line Plot of Speech Discrimination Threshold Over Time Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.1.6b	Bar Chart of the Frequency of Tinnitus at Each Timepoint Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.1.7b	Proportion of Responders (Improvement of 10 dB or more) in Pure Tone Audiometry Threshold Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.1.8.1b	Percent Change in Word Recognition Score at 80 dB and 60 dB in the Affected Ear Over Time Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.1.8.2b	Word Recognition Score at 80 and 60 dB in the Affected Ear Over Time Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.1.8.3b	Absolute Difference in Word Recognition Score between the Affected and Reference Ear at 80 and 60 dB Over Time Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.1.9b	Relationship of Time of Onset of Symptoms to First Study Drug Intake and the Primary Endpoint Part 2 – Intent-to-Treat Analysis Set	IP	
14.2.1.10b	Bar Chart of the Frequency of Vertigo at Each Timepoint Part 2 – Intent-to-Treat Analysis Set	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1b	Screen Failures Part 2 – All Screened Subjects	IP	
16.2.1.2b	Early Withdrawals Part 2 – All Randomized Subjects	IP	
16.2.1.3b	Inclusion and Exclusion Criteria – Screen Failures Part 2 – All Screened Subjects	IP	
16.2.2	**Protocol Deviations**		
16.2.2.1b	Protocol Deviations Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.3	**Subjects Excluded from the Efficacy Analyses**		
16.2.3.1b	Analysis Sets Part 2 – All Randomized Subjects	IP	
16.2.4	**Demographic Data**		
16.2.4.1b	Demographics Data Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.4.2b	Baseline Characteristics and Other Relevant Data Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.4.3b	Medical History Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.4.4b	Otologic History Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.4.5b	Ear, Neck, Nose and Throat Problems Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.4.6b	Baseline Pure Tone Audiometry Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.4.7b	Raw Data on Pure Tone Audiometry Part 1 – Intent-to-Treat Analysis Set		
16.2.5	**Compliance and/or Drug Concentration Data**		
16.2.5.1b	Prior, Study Concomitant and Study Treatment Concomitant Medications Part 1 – Safety Analysis Set	IP	
16.2.5.2b	Prior and Concomitant Oral Corticosteroids	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
	Part 2 – Safety Analysis Set		
16.2.5.3b	Study Treatment Exposure Part 2 – Safety Analysis Set	IP	
16.2.5.4b	PK Sample Collection Data Part 2 – Pharmacokinetic Analysis Set	IP	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1b	PTA Data Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.6.2b	Speech Discrimination Threshold Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.6.3b	Vertigo Data Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.6.4b	Tinnitus Severity Data Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.6.5b	Tinnitus Questionnaire Data Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.6.6b	DPOAE Data Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.6.7b	TEOAE Data Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.6.8b	EQ-5D-5L Data Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.6.9b	Word Recognition Data Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.6.10b	Biomarkers Data Part 2 – Intent-to-Treat Analysis Set	IP	
16.2.7	**Adverse Event Listings**		
16.2.7.1b	Adverse Events Part 2 – Safety Analysis Set	IP	
16.2.7.2b	Late Adverse Events Part 2 – Safety Analysis Set		
16.2.8	**Individual Laboratory Measurements and Other Safety**		
16.2.8.1b	Hematology Data Part 2 – Safety Analysis Set	IP	
16.2.8.2b	Serum Chemistry Data	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
	Part 2 – Safety Analysis Set		
16.2.8.3b	C-Reactive Protein Data Part 2 – Safety Analysis Set	IP	
16.2.8.4b	Pregnancy Test Data Part 2 – Safety Analysis Set	IP	
16.2.8.5b	Physical Examination Data Part 2 – Safety Analysis Set	IP	
16.2.8.6b	Vital Signs Data Part 2 – Safety Analysis Set	IP	
16.2.8.7b	Otoscopy Data Part 2 – Safety Analysis Set	IP	
16.2.8.8b	Tympanometry Data Part 2 – Safety Analysis Set	IP	
16.2.8.9b	Suicidality Assessment (C-SSRS) Part 2 – Safety Analysis Set	IP	