Statistical Analysis Plan

A Phase 2, Prospective, Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Multicenter Study to Evaluate the Efficacy of FX-322 Administered by Intratympanic Injection in Adults with Acquired Sensorineural Hearing Loss

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FX-322-208 Protocol (Version 3.0, 05 January 2022)

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STATISTICAL ANALYSIS PLAN
ACKNOWLEDGMENT AND SIGNATURE SHEET

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Approved: [redacted] Date: _____

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Version History

SAP Version	Approval Date	Change(s)	Rationale
1.0	26JUL2022	Not Applicable	Original Version
2.0	19JAN2023	Modified primary analysis as well as the fixed-sequence testing procedure. Clarified Words-in-Noise key secondary efficacy endpoint. Added Patient Global Impression of Change as key secondary efficacy endpoint. Specified estimands for primary and key secondary endpoints. Clarified methods for missing data for primary and key secondary endpoints. Updated the denominators for the disposition summary. Clarified speech reception threshold summary will be generated for treated and untreated ears. Stated randomization stratification factors since randomization complete at the time of SAP Version 2.0.	Version 2.0, finalized prior to database lock and treatment unblinding

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LIST OF ABBREVIATIONS

AC	Air Conduction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BC	Bone Conduction
BCA	Bone Conduction Average
BMI	Body Mass Index
BP	Blood Pressure
C-SSRS	Columbia-Suicide Severity Rating Scale
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CNC	Consonant-Nucleus-Consonant
CRF	Case Report Form
CSR	Clinical Study Report
dB	Decibel
EDC	Electronic Data Capture
EHFA	Extended High Frequency Audiometry
ET	Early Termination
FAS	Full Analysis Set
GEE	Generalized Estimating Equation
HL	Hearing Level
ICH	International Conference on Harmonisation
LOCF	Last observation carried forward
LS	Least Squares
MCAR	Missing Completely At Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model for Repeated Measures
NIHL	Noise-induced Sensorineural Hearing Loss
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PPAS	Per Protocol Analysis Set
PRO	Patient Reported Outcome
PT	Preferred Term
PTA	Pure Tone Average
[redacted]	[redacted]

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SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SfAS	Safety Analysis Set
SL	Sensation Level
SOC	System Organ Class
SPL	Sound Pressure Level
SNHL	Sensorineural Hearing Loss
SSNHL	Sudden Sensorineural Hearing Loss
SRT	Speech Reception Threshold
TEAE	Treatment-Emergent Adverse Event
TFI	Tinnitus Functional Index
WR	Word Recognition in Quiet
WIN	Words-in-Noise

1. PURPOSE OF THE ANALYSES

The purpose of this statistical analysis plan (SAP) is to provide detailed information to aid in the implementation of the statistical analysis and reporting of the study data for use in the clinical study report (CSR). It briefly summarizes the protocol, describes the analysis sets, and the planned analyses. The details of the specific statistical methods that will be used for the pre-specified analyses of the primary and secondary endpoints are provided and were defined prior to unblinding of the data. This SAP does not limit the analyses in the CSR, and additional analyses to supplement the CSR writing may be conducted and will be identified in the CSR as post hoc. Table, figure, and listing specifications are in separate documents.

This SAP was written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports and was finalized prior to database lock.

2. PROTOCOL SUMMARY

2.1. Study Objectives

Primary Objective

- To assess efficacy following a single dose of FX-322 versus Placebo, in subjects with acquired sensorineural hearing loss (SNHL).

Secondary Objective

- To assess safety following a single dose of FX-322 or Placebo in subjects with acquired sensorineural hearing loss.

2.2. Study Design

This is a Phase 2, prospective, randomized, double-blind, placebo-controlled, single-dose, multicenter study to evaluate the efficacy of FX-322, administered by intratympanic injection, in adults with acquired sensorineural hearing loss.

The study will have two Parts as described below:

Part A: Screening/Start of Lead-in/Visit 1, Lead-in/Visit 2

Part B: End of Lead-in/Treatment/Visit 3 (Day 1), Randomization (Double-blind), Follow-up (Days 30, 60 and 90), and Observation (Days 180 and 270)

2.2.1. Part A: Screening/Start of Lead-In/Visit 1, Lead-in/Visit 2

Visits can occur 30-40 days prior to study drug administration [Visit 3 (Day 1)]. All subjects will be evaluated to determine study eligibility. For the purpose of ensuring the integrity of the trial and minimizing bias, certain study design details are described within a restricted-access unmasked protocol addendum. As part of recording the medical history of subjects, concurrent use of hearing aids during the study will be documented, as well as hearing loss etiology and laterality (unilateral, bilateral). Eligible subjects will be required to return for Lead-in/ Visit 2 (14-18 days after Visit 1) to complete assessments. Subjects will be instructed to contact the Investigator or relevant staff if a medical change has occurred during the lead-in period (Visit 1 to pre-dose Visit 3). Eligible subjects will return for Visit 3 (Day 1) and will be evaluated to determine whether they meet appropriate Inclusion/Exclusion criteria required for randomization.

2.2.2. Part B: End of Lead-in/Treatment/Visit 3 (Day 1), Randomization (Double-blind), Follow-up (Days 30, 60 and 90), and Observation (Days 180 and 270)

Approximately 124 subjects are planned to be randomized in this study in order to obtain a target of 112 evaluable subjects. The subjects will be randomized to receive FX-322 or placebo according to the different treatment group assignments listed below:

Treatment Group	# of Subjects	Day 1
1	62	FX-322
2	62	Placebo

Once a subject has been identified as meeting all Inclusion/Exclusion criteria, including the criteria described within the unmasked protocol addendum which will be determined via the electronic data capture (EDC) system, the subject will be randomized. FX-322 or placebo will be administered at Visit 3 (Day 1). The syringes containing either placebo or FX-322 will be obscured to maintain the blind for the injecting Otolaryngologist.

Each subject will be placed in the supine position. Topical anesthesia (with the exception of phenol) will be administered directly to the tympanic membrane in the study ear. Under a microscope, a 25-gauge needle will be used to inject FX-322 or placebo into the middle ear at the junction of the posterior inferior and posterior superior quadrant with the needle tip directed towards the round window. The posterior superior quadrant should be avoided to prevent injury to the ossicles. After injection, the subject will continue to lie with the injected ear facing up for 20-30 minutes. The injections will be performed at an appropriate location designated by a Board-certified Otolaryngologist trained and experienced in performing intratympanic injections. Safety monitoring will include recording of adverse events (AEs), monitoring of audiology, tympanometry, otoscopic exams, and Columbia-Suicide Severity Rating Scale (C-SSRS) assessments.

Follow-up: Subjects will be required to return to clinic for safety, otologic, and audiologic assessments at Days 30 (Visit 4), 60 (Visit 5), and 90 (Visit 6) following the study injection. Unscheduled visits may occur as needed.

Observation: Subjects will return to clinic for safety, otologic, and audiologic assessments at Days 180 (Visit 7) and 270 (Visit 8).

2.3. Randomization

Subjects will be randomized in a 1:1 ratio to one of two groups (FX-322 or placebo, respectively). The randomization will be stratified for Visit 2 (Day -15) Maryland CNC Word Recognition Score (above or equal to 28% words in quiet correct and below 28% words in quiet correct) and unilateral versus bilateral hearing loss. A single injection of FX-322 or placebo will be administered on Day 1 by intratympanic injection in the study ear.

2.4. Study Population

Male and female adults (18-65 years inclusive), otherwise healthy with acquired sensorineural hearing loss, associated with noise-induced SNHL (NIHL) or idiopathic sudden SNHL (SSNHL).

2.5. Sample Size Determination

The sample size of 112 evaluable subjects, in a 1:1 allocation ratio of FX-322 and Placebo, was selected to provide an overall statistical power of at least 80% to detect a difference in the primary endpoint for word recognition, as defined by the proportion of subjects that exceed the 95% upper confidence limit as described by Carney and Schlauch (2007) in the study ear. The target enrollment of 124 subjects is an adjustment for an assumed 10% study dropout rate. Detailed sample size determination is provided in the unmasked protocol addendum. Each subject contributes one study ear and one non-study ear.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following is a list of general analysis and reporting conventions to be applied for this study.

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form n (%). If a count is 0, no percentage will be shown. To ensure completeness, summaries for categorical and discrete variables will include all categories, even if no subjects had a response in a particular category. Missing data for categorical variables will have a 'Missing' category added at the end and the count will be presented without a percentage. Percentages for categorical variables will exclude the 'Missing' category.

- Continuous variables will be summarized using number of evaluable subjects, mean, standard deviation (SD), minimum, maximum, and median. The mean, median, and

[redacted]

confidence intervals (CI) will be rounded and reported to 1 more level of precision than the original observations, and the SD will be rounded and reported to 2 more levels of precision than the original observations. The minimum and maximum will be the same precision as the original data.

- Following SAS default rules, the median will be reported as the rounded average of the two middle numbers if the dataset contains even numbers.

- P-values will be rounded and reported to 3 decimal places if greater than 0.001. If the rounded p-value is less than 0.001, '<0.001' will be reported. If the rounded p-value is >0.999, '>0.999' will be reported. P-values and significant levels will be reported as 0.05 rather than .05.

- No preliminary rounding will be performed; rounding will only occur after analysis. To round, consider digit to right of last significant digit: if < 5 then round down, if ≥5 then round up.

- All listings will be sorted in order of subject and time of assessment (e.g., visit, time, and/or event).

- Dates in listings will be displayed as yyyy-mm-dd (e.g., 2022-01-22).

- Age (in years) will be calculated using the date of birth and the Screening date in the following SAS algorithm: floor((intck('month', date of birth, Screening date) – (day(Screening date) < day(date of birth))))/12. In the analysis datasets, tables, and listings, age will be reported as the integer part of the derived age, with no rounding.

- For all efficacy endpoints, including word recognition in quiet (Maryland Consonant-Nucleus-Consonant [CNC] and W-22) and words in noise (WIN), baseline values for analysis will be defined by ear as the average across the pre-treatment timepoints (Lead-in and Day 1) for left and right ears separately. For the analyses of improvement from baseline above upper confidence limits, either per Carney-Schlauch (2007) or Thornton-Raffin (1978), the rounded up average will be used for conservative approach. Left and right ears will be mapped to treated and untreated for analysis.

- For all safety endpoints and other analyses, baseline will be the last non-missing value before study drug administration.

- For efficacy analyses, Day 90 values will be based on the scheduled Day 90 nominal case report form (CRF) recorded visit. If no scheduled visit data is available for the nominal day 90 CRF recorded visits, the non-missing data in either ear from an early termination or unscheduled assessment performed closest to the target day will be used.

- All endpoints which reference a change in percentage of recognized words are calculated as and should be interpreted as a linear change (i.e., observed – baseline) and not a relative change (i.e. (observed – baseline)/baseline x 100).

- For all shift from baseline analyses, percentages will be based on the number of subjects in each category at baseline and the post-baseline visit.

- All analysis will be performed using the SAS System version 9.4 or higher.

4. ANALYSIS SETS

Analysis sets in this study are defined in the following:

- Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects who receive one dose of study drug (regardless of whether a full dose was administered) in the study ear. Subjects will be analyzed according to their randomized treatment group.

- Per Protocol Analysis Set

The Per Protocol Analysis Set (PPAS) includes subjects in the FAS receiving one full dose of study drug in the study ear to be treated per the randomization treatment schedule and without major protocol deviations as defined in Section 6.1. PPAS subjects will be analyzed according to their randomized treatment group.

- Safety Analysis Set

The Safety Analysis Set (SfAS) includes all subjects who receive one dose of study drug (regardless of whether a full dose was administered) in any ear and will be analyzed according to the actual treatment received. For safety assessments completed by ear for each subject, results from actual treated and actual untreated ears will be summarized separately. The SfAS will be used for the analysis of safety.

All main efficacy analyses will be based on FAS, with sensitivity analyses for primary and key secondary endpoint analyses in the PPAS. If more than 10% of subjects in the FAS are excluded from the PPAS, additional sensitivity analyses, other than for the primary and key secondary endpoints based on PPAS, may be performed.

5. STUDY SUBJECTS

5.1. Disposition of Subjects

The disposition of all consented subjects will be tabulated by treatment group and overall. Subjects who failed screening or were not randomized will only be included in the overall column. The following disposition information will be summarized:

[redacted]

- The number of subjects consented (signed Informed Consent)
- The number and percentage of subjects who failed screening and the reasons for failure
- The number of subjects not randomized and the number of subjects randomized
- The number of subjects in the FAS
- The number and percentage of subjects in the PPAS and SfAS analysis sets
- The number and percentage of subjects who completed the study through Day 90 (Visit 6)
- The number and percentage of subjects who discontinued the study early and the reasons for withdrawal
- The number and percentage of subjects who discontinued the study early for reasons related to COVID-19
- The number and percentage of subjects who continued to the Observational period
- The number and percentage of subjects who completed Day 180 (Visit 7) and Day 270 (Visit 8)
- The number and percentage of subjects who did not complete Day 180 (Visit 7) and Day 270 (Visit 8) and the reasons not completed
- The number and percentage of subjects who did not complete Day 180 (Visit 7) and Day 270 (Visit 8) for reasons related to COVID-19

Percentages for the number of subjects who failed screening and the reasons for failure will be based on the number of consented subjects. All other percentages will be based on number of subjects in the SfAS.

Duration of study follow up (from randomization date to study completion date or early discontinuation visit date) will be summarized in a Kaplan-Meier curve for all randomized subjects by treatment group. Subjects who completed the study will be censored at the study completion date.

Subject disposition data for all randomized subjects will also be listed. A separate by-subject listing for screen failures will be generated along with reason for screen failure.

A listing of all subjects affected by the COVID-19 pandemic (discontinued the study early, had remote visits performed, or missed visits for reasons related due to COVID-19) will be provided to list the impacts of the pandemic on the subject's participation.

5.2. Demographic and Other Baseline Characteristics

Descriptive statistics for demographic and other baseline characteristics will be summarized by treatment group and overall based on FAS. Characteristics to be summarized include:

- Demographic: age, race, ethnicity, sex, height, weight, and body mass index (BMI)
- Hearing loss history: laterality, etiology of hearing loss for treated and untreated ears, duration of hearing loss for treated ears
- History of noise exposure
- Hearing aid use
- Pure Tone Average (0.5, 1, 2, and 4 kHz) for the treated ear
- Bone Conduction Average (0.5, 1, 2, and 4 kHz) for the treated ear
- Word Recognition in Quiet (Maryland CNC) score for the treated ear
- Word Recognition in Quiet (W-22) score for the treated ear
- WIN score for the treated ear
- Patient Global Impression of Severity (PGI-S) Hearing Loss response
- Patient Global Impression of Severity (PGI-S) Daily Impacts response
- Randomization stratum

Demographic and baseline characteristics data will be listed for subjects in the FAS.

6. STUDY OPERATIONS

6.1. Study Conduct

Enrollment will be summarized by site for all enrolled, randomized, and treated subjects, separately. A by-subject listing of batch numbers for all treated subjects will be provided.

The number and percentage of study visits attended will be summarized for subjects in the FAS.

6.2. Protocol Deviations

Protocol deviations will be identified, documented, reviewed, and assessed according to the study protocol deviation guidance. Important or major protocol deviations are those that

might significantly affect the completeness, accuracy, and/or reliability of key study data or that might significantly affect a subject's rights, safety, or well-being.

Major protocol deviations will be listed and tabulated by deviation category for subjects in the FAS by treatment group and overall.

7. ENDPOINT EVALUATION

7.1. Overview of Analysis Methods

7.1.1. Pooling Algorithm

This is a multi-center (US only) study. Unless stated otherwise, data from all participating centers in the study will be pooled for analyses. A site poolability assessment of the primary efficacy analysis will be conducted to assess heterogeneity of the treatment effect between sites. This will be conducted as a descriptive analysis for the primary efficacy endpoint.

7.1.2. Assessment Time Windows

For by-visit summaries, the nominal visit will be used for analysis. Unscheduled visits will be listed but will not be displayed separately in the summaries.

Analysis windows listed in Table 7-1 will be used in the efficacy analyses for slotting actual efficacy assessment date into planned assessment schedule. Early termination visit and unscheduled visit efficacy data will be included in the analyses if no scheduled visit data is available for the nominal CRF visit. If more than one unscheduled assessment (early termination or unscheduled) is performed within an analysis window, the assessment performed closest to the target day will be used.

Table 7-1 Study Visit Windows

Visit	Visit Number	Assessment /Day	Target Day	Target Window	Analysis Window[a]
Screening/ Start of Lead-In	1	-40 to -30	N/A	N/A	N/A - Nominal CRF visit
Lead-In Visit	2	-26 to -12	Visit 1 + 16 days	Target day (+/- 2 days)	N/A - Nominal CRF visit
End of Lead-In/ Treatment	3	1	Visit 1 + 35 days	1/Target day (+/- 5 days)	1
In-Clinic Follow-up	4	30	30	25-35 (+/- 5 days)	2-45
In-Clinic Follow-up	5	60	60	55-65 (+/- 5 days)	46-75

In-Clinic Follow-up /Early Termination (ET)	6	90	90	85-95 (+/- 5 days)	76-135
In-Clinic Observation	7	180	180	173-187 (+/- 7 days)	136-225
In-Clinic Observation	8	270	270	263-277 (+/- 7 days)	≥226
[a]Analysis windows for the Screening and Lead-In Visit are not defined and visit assignments are based on the nominal CRF visits. Analysis windows for visits on or after randomization are defined using the mid-points between each scheduled visit and will be used to map early termination or unscheduled visit data to scheduled visits.					

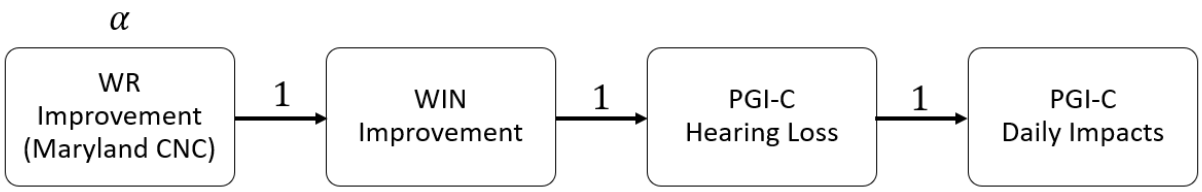
7.1.3. Timing of Analyses

Primary efficacy analysis will be conducted after all subjects have either completed the follow-up visits (Day 30, 60, and 90 visits) or early discontinued from study. Primary analysis will be performed in an unblinded fashion for analysis purposes while subjects not completing the observation visits will continue to be followed as being blinded to treatment assignment. Final CSR analyses will be performed after the study is completed, and the database is locked.

7.1.4. Multiplicity Adjustment

A fixed-sequence testing procedure will be implemented to control the family-wise type I error rate at 5% for the primary and key secondary endpoints as presented graphically in Figure 1. The hypothesis of superiority on the primary and key secondary efficacy endpoints of FX-322 versus placebo will be tested in the hierarchical order. The primary efficacy endpoint, incidence of subjects who have a Word Recognition in Quiet (Maryland CNC) improvement at Day 90, will be tested first, using the primary analysis approach described in Section 7.3.1. If superiority of FX-322 over placebo in improving speech perception for Word recognition in Quiet (WR) is established, the treatment effect in the key secondary endpoint, WIN improvement based on mean change from baseline in percentage of recognized words overall at Day 90, will be tested subsequently, using the analysis approach described in Section 7.4.2. If superiority of FX-322 over placebo is established for the key secondary endpoint, the treatment effect the next key secondary efficacy endpoint, Patient Global Impression of Change (PGI-C) Hearing Loss Scale responses at Day 90, will be tested subsequently, using the analysis approach described in Section 7.5.2. Lastly, if superiority of FX-322 over placebo is established for the previous three endpoints, the treatment effect for PGI-C Daily Impacts Scale responses at Day 90 will be tested subsequently, using the analysis approach described in Section 7.5.4.

Figure 1 - Multiple Comparisons Procedure for Primary and Key Secondary Endpoints



7.1.5. Model Fitting

Inferential statistical methods examining continuous endpoints will be examined via a Mixed-effects Model for Repeated Measures (MMRM). Inferential analyses for categorical endpoints will be analyzed using univariate methods and/or Generalized Estimating Equations (GEE). The MMRM and GEE analyses will employ an unstructured working correlation matrix.

Further details for each of the planned models and analyses are provided in subsequent sections.

7.1.6. Imputation Rules for Partial/Missing Data

Based on previous studies of FX-322, there is expected to be a very minimal amount of missing data in this study. Missing data for endpoints for word recognition in quiet using Carney-Schlauch confidence intervals will be assumed missing at random and will be imputed using the last observation carried forward (LOCF). Missing data for the key secondary endpoint for WIN improvement will be assumed missing at random and will be taken into account using the model-based MMRM approach. Missing data for PGI-C analyses will not be imputed. Missing data for other endpoints will remain missing in the planned statistical summaries and analyses.

7.1.7. Summary of Endpoints and Analysis Methods

To assess treatment effect if no rescue medication is available, for efficacy analyses, assessments performed on or after date of rescue medication or therapy taken during the follow up period will not be included in the analyses. Specifically, rescue medication includes intratympanic steroid administered in the treated ear after study drug administration through Day 90 visit. A summary of endpoints and analysis methods is presented in Table 7-2.

Table 7-2 Endpoints and Analysis Methods

Endpoint	Analysis Method(s)	Section
Word Recognition in Quiet (Maryland CNC) and Word Recognition (W-22)*		7.3

Endpoint	Analysis Method(s)	Section
Improvement from baseline above Carney-Schlauch upper confidence limits (Primary Endpoint)	• Descriptive summary for treated and untreated ears • Primary Analysis: Chi-Square test for treated ears • Sensitivity Analysis: Chi-Square test for treated ears in PPAS • Sensitivity Analysis: Chi-Square test for treated ears based on improvement from baseline above 80%, 85%, and 90% Carney-Schlauch upper confidence limits • Sensitivity Analysis: CMH test for treated ears • Sensitivity Analysis: GEE in treated ears • Sensitivity Analysis: DerSimonian and Laird (1986) estimation for treated ears using both randomization factors (4 strata) as defined in Section 2.3. If the analysis cannot be computed using both randomization factors, the analysis will be performed using the single randomization factor (2 strata) that produces more similarly sized strata. • Scatterplots for treated and untreated ears • Descriptive summary for treated ears by site	7.3.1
Percentage of recognized words	• Descriptive summary for treated and untreated ears	7.3.2
Change from baseline in percentage of recognized words	• Descriptive summary for treated and untreated ears • Line graphs (with standard error bars) for observed mean change from baseline for treated ears	7.3.3
Improvement ≥10% (5 words) from baseline in percentage of recognized words	• Descriptive summary for treated ears • GEE in treated ears	7.3.4
Change from baseline in arcsine-transformed WR	• Line graphs (with standard error bars) for adjusted least squared means in change from baseline for treated ears • MMRM in treated ears	7.3.5
Improvement from baseline above Thornton-Raffin upper confidence limits	• Descriptive summary for treated and untreated ears • Scatterplots for treated and untreated ears	7.3.6
Words-In-Noise*		7.4
Percentage of recognized words	• Descriptive summary for treated and untreated ears	7.4.1
Change from baseline in percentage of recognized	• Descriptive summary for treated and untreated ears	7.4.2

Endpoint	Analysis Method(s)	Section
words (Key Secondary Efficacy Endpoint)	• Line graphs (with standard error bars) for adjusted least squared means in change from baseline for treated ears • Primary Analysis: MMRM in treated ears • Sensitivity Analysis: MMRM in treated ears for PPAS	
Improvement ≥10% (7 words) from baseline in percentage of recognized words	• Descriptive summary for treated ears • GEE in treated ears	7.4.3
Spearman-Kärber estimates of decibel (dB) thresholds for word recognition (25th, 50th (median) and 75th percentiles)	• Descriptive summary for treated ears • Scatter plots for treated ears	7.4.4
Change from baseline in median Spearman-Kärber estimates	• Descriptive summary for treated ears • Line graphs (with standard error bars) for adjusted least squared means in change from baseline for treated ears • MMRM in treated ears	7.4.5
Improvement ≥3 dB shifts in median Spearman-Kärber estimates from baseline	• Descriptive summary for treated ears • GEE in treated ears	7.4.6
Patient Global Impression of Severity and Patient Global Impression of Change*		7.5
PGI-S hearing loss scale responses	• Descriptive summary for treated ears	7.5.1
PGI-C hearing loss scale responses (Key Secondary Efficacy Endpoint)	• Analysis of Covariance (ANCOVA) in treated ears	7.5.2
PGI-S daily impacts scale responses	• Descriptive summary for treated ears	7.5.3
PGI-C daily impacts scale responses (Key Secondary Efficacy Endpoint)	• ANCOVA in treated ears	7.5.4
Pure Tone Audiometry		7.6
Air Conduction (AC) and Bone Conduction (BC) audiometry dB hearing level (HL) thresholds by frequency	• Descriptive summary for treated and untreated ears	7.6.1

Endpoint	Analysis Method(s)	Section
Mean overall pure tone average (PTA) (AC over 0.5, 1, 2, and 4 kHz) and Bone Conduction Average (BCA) (BC over 0.5, 1, 2 and 4 kHz)	• Descriptive summary for treated ears	7.6.2
AC and BC improvement ≥10 and ≥15 dB HL from baseline, separately, for two contiguous frequencies	• Descriptive summary for treated ears	7.6.3
AC and BC improvement ≥15 and ≥20 dB HL from baseline, separately, for any frequency	• Descriptive summary for treated ears	7.6.4
AC and BC composite improvement from baseline	• Descriptive summary for treated ears • GEE in treated ears	7.6.5
Change from baseline in mean overall PTA and BCA	• Descriptive summary for treated ears	7.6.6
Shift from baseline in mean overall PTA categories	• Descriptive summary for treated ears	7.6.7
Mean low AC dB HL threshold (AC only over 0.25, 0.5, 1, and 2 kHz frequencies)	• Descriptive summary for treated ears	7.6.8
Mean high AC dB HL threshold (AC only over 3, 4, 6, and 8 kHz frequencies)	• Descriptive summary for treated ears	7.6.9
Air-Bone Imbalance at 0.5, 1, 2, 3, and 4 kHz	• Descriptive summaries for treated ears	7.6.10
Shift from baseline in Air-Bone Imbalance at 0.5, 1, 2, 3, and 4 kHz	• Descriptive summary for treated ears	7.6.11
Extended High Frequency Audiometry (EHFA)		7.7
AC audiometry dB HL thresholds by frequency	• Descriptive summary for treated and untreated ears	7.7.1
Mean dB HL threshold (AC over 9-16 kHz)	• Descriptive summary for treated ears	7.7.2
AC improvement ≥10 and ≥15 dB HL from baseline,	• Descriptive summary for treated ears	7.7.3

Endpoint	Analysis Method(s)	Section
separately, for two contiguous frequencies		
AC improvement ≥15 and ≥20 dB HL from baseline, separately, for any frequency	• Descriptive summary for treated ears	7.7.4
AC composite improvement from baseline	• Descriptive summary for treated ears • GEE in treated ears	7.7.5
Shift from baseline of no signal to any signal by frequency	• Descriptive summary for treated ears	7.7.6
Shift from baseline of no signal to any signal in two contiguous frequencies	• Descriptive summary for treated ears	7.7.7
Shift from baseline of no signal to any signal in three contiguous frequencies	• Descriptive summary for treated ears	7.7.8
Examination of Subgroups*		7.8
Incidence of WR Improvement from baseline above Carney-Schlauch upper confidence limits	• Forest plot	

*Efficacy endpoint

7.2. Primary and Key Secondary Efficacy Endpoint Estimands

7.2.1. Primary Efficacy Endpoint

Variable: Response, defined as improvement from baseline at Day 90 above Carney-Schlauch 95% upper confidence limits in Word Recognition in Quiet (Maryland CNC) in treated ears.

Population: The analysis population will be the FAS.

Intercurrent events: Subjects who discontinue the study early will be considered missing at random, and their last non-missing observation will be carried forward (i.e., if their Day 60 improvement is above Carney-Schlauch 95% upper confidence limit, then their Day 90 results will be assumed to also be above the limit).

Population-level summary: Comparison of responder proportions between treatment groups at the Day 90 visit.

Additional details on the computation, analysis, and sensitivity analyses for the primary endpoint can be found in Section 7.3.1.

7.2.2. Key Secondary Efficacy Endpoint

Variable: Change from baseline in percentage of recognized words overall at Day 90 in Words-in-Noise in treated ears.

Population: The analysis population will be the FAS.

Intercurrent events: Subjects who discontinue the study early will be assumed missing at random and missing responses will be taken into account using the model-based approach of MMRM.

Population-level summary: Comparison of mean difference between treatment groups at the Day 90 visit in change from baseline in percentage of recognized words.

Additional details on the computation, analysis, and sensitivity analyses for the key secondary efficacy endpoint can be found in Section 7.4.2.

7.2.3. Other Key Secondary Efficacy Endpoints

Variables: PGI-C hearing loss scale response and PGI-C daily impacts scale response at Day 90.

Population: The analysis population will be the FAS.

Intercurrent events: Subjects who do not have these assessments completed at Day 90 will be assumed missing at random, and no responses will be imputed.

Population-level summary: Comparison of mean difference between treatment groups at the Day 90 visit.

Additional details on the computation, analysis, and sensitivity analyses for these secondary efficacy endpoints can be found in Section 7.5.2 and 7.5.4.

7.3. Word Recognition in Quiet: Maryland CNC and W-22

Word recognition will be measured separately with recorded Maryland CNC and W-22 word lists. Both tests will consist of 50 words presented to the subject and the percentage of words correctly identified will be recorded separately for each test. If all 50 words are not assessed in an ear, the WR test score will not be calculated for that ear.

Word recognition will be performed at the Screening/Start of Lead-In, Lead-In, End of Lead-In/Treatment, Day 30, Day 60, Day 90, Day 180, and Day 270 visits. For Screening/Start of Lead-In, testing will be performed at 30 dB sensation level (SL) regarding the pure tone average of 0.5, 1, and 2 kHz at Screening/Start of Lead-In. For Lead-In and all subsequent visits (End of Lead-In/Treatment, Day 30, Day 60, Day 90, Day 180, and Day 270) testing will be performed at 30 dB SL regarding the pure tone average of 0.5, 1, and 2 kHz at Lead-In. If 30 dB SL is at an uncomfortable listening level for the participant, testing will be performed at the participant's most comfortable listening level. Word lists will be rotated at each visit.

For speech perception, WR in Quiet (Maryland CNC) will be used for the primary analyses. All analyses will be repeated using WR in Quiet (W-22) for supplementary analyses.

Word Recognition in Quiet results will be presented in a data listing for subjects in the FAS.

7.3.1. Improvement from baseline above Carney-Schlauch upper confidence limits

- *Computation of the Endpoint*

Improvement is defined as an increase in post-baseline WR score above the Carney-Schlauch (2007) 95% upper limit based on baseline (average of Lead-In and End of Lead-In/Treatment scores) assessment. Subjects with improvement will be computed as 1, and as 0, otherwise for each visit and by ear (left, right). Missing values will be imputed using LOCF. Left and right ears will be mapped to treated and untreated for analysis. The incidence of WR improvement will be computed as the proportion of subjects who have a WR in Quiet improvement.

The Carney-Schlauch 95% confidence intervals (2007) reported in Section 14.2 will be used directly and not computed.

- *Analysis of the Endpoint*

The incidence of WR improvement will be summarized descriptively for treated and untreated ears separately by visit and treatment group for subjects in the FAS.

The primary efficacy analysis will be conducted for the incidence of WR improvement at Day 90 in treated ears for subjects in the FAS using a 1 degree of freedom Chi-Square test for a single 2x2 table without stratification. Although the randomization was stratified by Visit 2 WR Maryland CNC score (>= 28% vs < 28%) and laterality of hearing loss (bilateral vs unilateral), the randomization was done to maintain balance among the treatment groups across the randomization factors to help interpretation of the results rather than any prognostic status. As such, it is believed the unstratified primary analysis will be more straightforward in interpretation, especially if some of the sample sizes in individual strata are small.

- *Sensitivity Analyses of the Endpoint*

The Chi-Square test will be repeated using treated ears for subjects in the PPAS. Additionally, the Chi-Square test will be performed with improvement being defined as an increase in post-baseline WR score above the 90%, 85%, and 80% upper limit based on baseline assessment using Carney-Schlauch method for treated ears. The 90%, 85%, and 80% upper limits will be determined based on simulation using the same approach used to compute the 95% limits described by Carney-Schlauch (2007).

A two-sided 95% CI for the odds ratio for the incidence of improvement between the treatment groups for treated ears will also be computed using the Cochran-Mantel-Haenszel (CMH) chi-square test, adjusted for the randomization stratification factors.

A GEE model will be utilized to estimate an odds ratio and its associated 95% CI between the treatment groups at each visit for treated ears. With the binomial distribution assumption and logit link, the model will include fixed effects of treatment group, visit, interaction between visit and treatment group, baseline WR score, interaction between baseline WR score and visit, and randomization stratification factors. The model will utilize an unstructured working correlation matrix. If the model fails to converge, the randomization stratification factors will be excluded from the model. The odds ratios along with 95% CIs and p-values between treatment groups will be reported by visit.

An analysis will be conducted for the incidence of WR improvement at Day 90 using the DerSimonian and Laird method. In treated ears only for subjects in the FAS, a 2-sided 95% CI for the difference between treatment groups in incidence of WR improvement at Day 90 will be computed by the method of DerSimonian and Laird, using a fixed-effects model (setting the variance in treatment effects, Δ^2, equal to zero), adjusting for the randomization stratification factors. The weighted difference in the incidence of improvement, 95% CI, and p-value can be determined by the following formula:

$$\hat{\theta} = \frac{\sum_{i=1}^{4} w_i \hat{\theta}_i}{\sum_{i=1}^{4} w_i} \sim N(\theta, 1/\sum_{i=1}^{4} w_i)$$

Where $\hat{\theta}_i$ is the difference in the incidence of improvement at Day 90 of the ith stratum and $w_i = 1/\mathrm{var}(\hat{\theta}_i)$. The DerSimonian and Laird methodology is consistent with inverse variance weighting methodology. If the analysis cannot be performed using both randomization factors (4 strata) due to no variation within 1 or more randomization strata, the analysis will be performed using the single randomization factor (2 strata) that produces more similarly sized strata. Scatter plots displaying the percentage of recognized words (Section 7.3.2) at baseline versus post-baseline, along with the Carney-Schlauch confidence intervals, will be generated for each visit separately for treated and untreated ears.

7.3.2. Percentage of recognized words

- *Computation of the Endpoint*

The percentage of recognized words will be computed by visit as the number of recognized words divided by 50 and multiplied by 100, separately for each ear. Missing data will not be imputed.

- *Analysis of the Endpoint*

The percentage of recognized words will be summarized descriptively for treated and untreated ears separately by visit and treatment group for subjects in the FAS.

7.3.3. Change from baseline in percentage of recognized words

- *Computation of the Endpoint*

The change from baseline to each post-baseline visit in percentage of recognized words will be computed as 100*[(w/50) – (b/50)] where "w" is the frequency of words recognized at the post-baseline visit and "b" is the frequency of words recognized at baseline.

- *Analysis of the Endpoint*

The change from baseline in percentage of recognized words will be summarized descriptively for treated and untreated ears separately by visit and treatment group for subjects in the FAS.

A Line graph (with standard error bars) will be created for the observed mean change from baseline in percentage of recognized words for treated ears by post-baseline visit and treatment group for subjects in the FAS. Post-baseline visit will be plotted on the x-axis and the observed mean change from baseline in percentage of recognized words for treated ears will be plotted on the y-axis. Each treatment group will be presented as a separate line in the plot.

7.3.4. Improvement ≥10% (5 words) from baseline in percentage of recognized words

- *Computation of the Endpoint*

Improvement ≥10% in percentage of recognized words at each post-baseline visit for treated ears will be computed as 1 if the change from baseline in percentage of recognized words ≥10% and as 0, otherwise where change from baseline is non-missing. Missing data will not be imputed.

- *Analysis of the Endpoint*

The incidence of improvement ≥10% in percentage of recognized words at each post-baseline visit for treated ears will be summarized using frequencies and percentages by visit and treatment group for subjects in the FAS.

In treated ears only for subjects in the FAS, the GEE model described in Section 7.3.1 will be repeated for improvement ≥10% in percentage of recognized words.

7.3.5. Change from Baseline in Arcsine-transformed WR

- *Computation of the Endpoint*

The arcsine-transformed WR (Studebaker, 1985) will be computed by visit for treated ears as

$$R = arcsin\sqrt{w/(n+1)} + arcsin\sqrt{(w+1)/(n+1)}$$

where "R" is the transformed radians, "w" is the frequency of words recognized, and "n" is the number of words in the word test (n = 50 for WR assessments). Missing data will not be imputed.

Change from baseline to each post-baseline visit in arcsine-transformed WR will be computed as R post-baseline – R at baseline.

- *Analysis of the Endpoint*

In treated ears only for subjects in the FAS, post-baseline treatment group comparisons through day 90 will be performed using a MMRM model for change from baseline in arcsine-transformed WR with fixed covariates for treatment group, visit, interaction between visit and treatment group, baseline WR score, the interaction between baseline WR score and visit, and randomization stratification factors. If the model fails to converge, the randomization stratification factors will be removed from the model. An unstructured covariance will be used to model the within-subject errors. Linear contrasts will be constructed to estimate the treatment effect for the mean change from baseline in arcsine-transformed WR by visit (e.g., estimated Least squares (LS) Mean differences by visit).

A Line graph (with standard error bars) will be created for the adjusted (least squares) mean change from baseline in arcsine-transformed WR for treated ears by post-baseline visits through day 90 and treatment group for subjects in the FAS. Post-baseline visit will be plotted on the x-axis and the adjusted (least squares) mean change from baseline in arcsine-transformed WR for treated ears will be plotted on the y-axis. Each treatment group will be presented as a separate line in the plot.

7.3.6. Improvement from baseline above Thornton-Raffin upper confidence limits

- *Computation of the Endpoint*

Improvement is defined as an increase in post-baseline WR score above the Thornton-Raffin (1978) 95% upper limit (Section 14.1) based on baseline (average of Lead-In and End of Lead-In/Treatment scores) assessment. Subjects with improvement will be computed as 1, and as 0, otherwise for each visit and by ear (left, right). Missing data will not be imputed. Left and right ears will be mapped to treated and untreated for analysis. The incidence of WR improvement will be computed as proportion of subjects who have a WR in Quiet improvement based on the Thornton-Raffin confidence limits.

The Thornton-Raffin 95% confidence intervals reported in Section 14.1 will be used directly and not computed.

- *Analysis of the Endpoint*

The incidence of WR improvement will be summarized descriptively for treated and untreated ears separately by visit and treatment group for subjects in the FAS.

Scatter plots displaying the percentage of recognized words (Section 7.3.2) at baseline versus those at post-baseline, along with the Thornton-Raffin confidence intervals, will be generated for each visit separately for treated and untreated ears.

7.4. Words-In-Noise

The WIN test, using the NU-6 list, was developed as an instrument to quantify the ability of listeners to understand monosyllabic words in background noise using multitalker babble (Wilson, 2003). Materials are recorded at 7 signal-to-noise ratios (0, 4, 8, 12, 16, 20, 24 dB) that are presented in a descending manner. This test is conducted by presenting 2 lists of 35 recorded words (70 total) to each ear. The number of and percentage of correctly recognized words at each signal-to-noise ratio will be recorded separately by ear. The overall WIN score will be recorded as the percentage of correctly recognized words across all signal-to-noise ratios by visit and ear. If all 70 words are not assessed in each ear, the WIN test score will not be calculated. This test will occur at the Screening/Start of Lead-In, Lead-In, End of Lead-In/Treatment, Day 30, Day 60, Day 90, Day 180, and Day 270 visits. Testing will be performed at 80 dB sound pressure level (SPL). Word lists will be rotated at each visit.

WIN results will be presented in a data listing for the FAS.

7.4.1. Percentage of recognized words

- *Computation of the Endpoint*

At each visit and by ear (left, right), the number of words classified as correctly recognized at each signal-to-noise ratio will be recorded. The overall WIN score will also be computed as the number of words correctly recognized across all signal-to-noise ratios. Left and right ears will be mapped to treated and untreated for analysis. The percentage of recognized words will be computed for each signal-to-noise ratio by visit as the number of recognized words divided by 10 and multiplied by 100, separately for each ear. The percentage of recognized words overall by visit will be computed as the number of recognized words divided by 70 and multiplied by 100, separately for each ear.

- *Analysis of the Endpoint*

7.4.2. The percentage of recognized words at each signal-to-noise ratio and overall will be summarized descriptively for treated and untreated ears separately by visit

and treatment group for subjects in the FAS.Change from baseline in percentage of recognized words

- *Computation of the Endpoint*

The change from baseline to each post-baseline visit in percentage of recognized words at each signal-to-noise ratio will be computed as 100*[(w/10) – (b/10)] where "w" is the frequency of words recognized at the post-baseline visit and "b" is the frequency of words recognized at baseline. The change from baseline to each post-baseline visit in percentage of recognized words overall will be computed using the same algorithm, but with 70 words in the denominator instead of 10. Missing data will not be imputed.

- *Analysis of the Endpoint*

The change from baseline in percentage of recognized words at each signal-to-noise ratio and overall will be summarized descriptively for treated and untreated ears separately by visit and treatment group for subjects in the FAS.

The primary analysis for the key secondary endpoint, WIN improvement based on mean change from baseline in percentage of recognized words overall at Day 90, will be based on the following MMRM model. In treated ears only for subjects in the FAS, post-baseline treatment group comparisons through day 90 will be performed using a MMRM model for change from baseline in percentage of recognized words overall with fixed covariates for treatment group, visit, interaction between visit and treatment group, baseline WIN score overall, the interaction between baseline WIN score overall and visit, and randomization stratification factors. If the model fails to converge, the randomization stratification factors will be removed from the model. An unstructured covariance will be used to model the within-subject errors. Linear contrasts will be constructed to estimate the treatment effect for the mean change from baseline in percentage of recognized words overall by visit (e.g., estimated Least squares (LS) Mean differences by visit).

Line graphs (with standard error bars) will be created for the adjusted (least squares) mean change from baseline in percentage of recognized words overall estimates for treated ears by post-baseline visit and treatment group for subjects in the FAS. Post-baseline visit will be plotted on the x-axis and the adjusted (least squares) mean change from baseline in percentage of recognized words overall estimates for treated ears will be plotted on the y-axis. Each treatment group will be presented as a separate line in the plot.

- *Sensitivity Analyses of the Endpoint*

The MMRM will be repeated using treated ears for subjects in the PPAS.

7.4.3. Improvement ≥10% (7 words) from baseline in percentage of recognized words overall

- *Computation of the Endpoint*

Improvement ≥10% from baseline in percentage of recognized words overall at each post-baseline visit for treated ears will be computed as 1 if the change from baseline in percentage of recognized words overall ≥10% and as 0, otherwise where the change is not missing. Missing data will not be imputed. Improvement ≥10% (7 words) from baseline in percentage of recognized words will not be computed for each signal-to-noise ratio.

- *Analysis of the Endpoint*

The incidence of improvement ≥10% from baseline in percentage of recognized words overall at each post-baseline visit for treated ears will be summarized using frequencies and percentages by visit and treatment group for subjects in the FAS.

In treated ears only for subjects in the FAS, post-baseline treatment group comparisons for incidence of improvement ≥10% from baseline in percentage of recognized words overall will be analyzed using a GEE model. With the binomial distribution assumption and logit link, the model will include fixed effects of treatment group, visit, interaction between visit and treatment group, baseline WIN score, interaction between baseline WIN score and visit, and randomization stratification factors. If the model fails to converge, the randomization stratification factors will be excluded from the model. The odds ratios along with 95% CIs and p-values between treatment groups will be reported by visit.

7.4.4. Spearman-Kärber estimates of dB thresholds for word recognition (25th, 50th (median) and 75th percentiles)

- *Computation of the Endpoint*

The Spearman-Kärber estimates (25th, 50th (median) and 75th percentiles) of dB thresholds for word recognition (Wilson et al., 1973) at each visit for treated ears will be computed as

$$dB = i + (p_c * d) - (d * w)/c$$

where "p_c" is the percentile of interest, "i" is the initial dB presentation level (fixed at 24), "d" is the attenuation dB step size (fixed at 4), "c" is the number of words per decrement (fixed at 10), and "w" is the frequency of words recognized overall at each visit. Missing data will not be imputed.

- *Analysis of the Endpoint*

Spearman-Kärber estimates (25th, 50th (median) and 75th percentiles) will be summarized descriptively for treated ears by visit and treatment group for subjects in the FAS.

For each post-baseline visit, scatter plots of the median Spearman-Kärber estimates at baseline versus the post-baseline visit will be produced for treated ears by treatment group for subjects in the FAS.

7.4.5. Change from baseline in median Spearman-Kärber estimates

- *Computation of the Endpoint*

Change from baseline to each post-baseline visit in median Spearman-Kärber estimates will be computed as dB post-baseline – dB at baseline. Missing data will not be imputed.

- *Analysis of the Endpoint*

The change from baseline in median Spearman-Kärber estimates will be summarized descriptively for treated ears by visit and treatment group for subjects in the FAS.

In treated ears only for subjects in the FAS, post-baseline treatment group comparisons through day 90 for the change from baseline in median Spearman-Kärber estimate will be analyzed using a MMRM model. The model will include fixed covariates of treatment group, visit, interaction between visit and treatment group, baseline median Spearman-Kärber estimate, interaction between baseline median Spearman-Kärber estimate and visit, and randomization stratification factors. If the model fails to converge, the randomization stratification factors will be dropped from the model. An unstructured covariance will be used to model the within-subject errors. Linear contrasts will be constructed to estimate the treatment effect on the mean change from baseline in median Spearsman-Kärber estimate by visit (e.g., estimated LS Mean differences by visit).

Line graphs (with standard error bars) will be created for the adjusted (least squares) mean change from baseline in median Spearman-Kärber estimates for treated ears by post-baseline visit and treatment group for subjects in the FAS. Post-baseline visit will be plotted on the x-axis and the adjusted (least squares) mean change from baseline in median Spearman-Kärber estimates for treated ears will be plotted on the y-axis. Each treatment group will be presented as a separate line in the plot.

7.4.6. Improvement ≥3 dB shifts in median Spearman-Kärber estimates from baseline

- *Computation of the Endpoint*

Improvement ≥ 3 dB shifts in median Spearman-Kärber estimates at each post-baseline visit for treated ears will be computed as 1 if the post-baseline Spearman-Kärber estimate – baseline Spearman-Kärber estimate is ≥3 and as 0, otherwise where the baseline and post-baseline Spearman-Kärber estimates are not missing. Missing data will not be imputed.

- *Analysis of the Endpoint*

The incidence of improvement ≥3 dB shifts in median Spearman-Kärber estimates at each post-baseline visit for treated ears will be summarized using frequencies and percentages by visit and treatment group for subjects in the FAS.

Post-baseline treatment group comparisons will be performed using the GEE model described in Section 7.4.3 for subjects in the FAS.

[redacted]

7.5. Patient Global Impression of Severity/Patient Global Impression of Change

PGI-S Hearing Loss Scale, administered at the End of Lead-In/Treatment visit, is a patient reported outcome (PRO) measure for subjects to best describe the severity of their hearing loss over the past week.

PGI-C Hearing Loss Scale, administered at the Day 90 visit, is a PRO measure to describe the overall change in their hearing loss after study drug administration.

PGI-S Daily Impacts Scale, administered at the End of Lead-In/Treatment visit, is a PRO measure for subjects to best describe the impact of their hearing loss on daily activities.

PGI-C Daily Impacts Scale, administered at the Day 90 visit, is a PRO measure to describe the overall change in the impact of their hearing loss on daily activities since study drug administration.

7.5.1. PGI-S hearing loss scale responses

- *Computation of the Endpoint*

Categories will be assigned to numeric values as follows: “None” = 1, “Mild” = 2, “Moderate” = 3, “Severe” = 4, and “Very Severe” = 5.

- *Analysis of the Endpoint*

The number and of percentage of subjects in each category (“None”, “Mild”, “Moderate”, “Severe”, “Very Severe”) in PGI-S hearing loss scale will be summarized descriptively by treatment group for subjects in the FAS. The numeric values will be used as a covariate for analyzing the PGI-C hearing loss scale.

7.5.2. PGI-C hearing loss scale responses

- *Computation of the Endpoint*

Categories will be assigned to numeric values as follows: “Much better” = 1, “A little better” = 2, “No change” = 3, “A little worse” = 4, and “Much worse” = 5.

- *Analysis of the Endpoint*

The number and of percentage of subjects in each category (“Much better”, “A little better”, “No change”, “A little worse”, “Much worse”) in PGI-C hearing loss scale will be summarized descriptively by treatment group for subjects in the FAS.

Additionally, as a key secondary efficacy analysis, the average response in PGI-C hearing loss scale, using the assigned numeric values of 1-5, will be compared between treatment groups at Day 90. An ANCOVA model, adjusting for the subject’s baseline PGI-S hearing loss

scale category as a quantitative covariate using the assigned numeric values of 1-5, will be used. Subjects with missing data at Day 90 will be excluded from analysis.

7.5.3. PGI-S daily impacts scale responses

- *Computation of the Endpoint*

Categories will be assigned to numeric values as follows: “None” = 1, “Mild” = 2, “Moderate” = 3, “Severe” = 4, and “Very Severe” = 5.

- *Analysis of the Endpoint*

The number and of percentage of subjects in each category (“None”, “Mild”, “Moderate”, “Severe”, “Very Severe”) in PGI-S daily impacts scale will be summarized descriptively by treatment group for subjects in the FAS. The numeric values will be used as a covariate for analyzing PGI-C daily impacts scale.

7.5.4. PGI-C daily impacts scale responses

- *Computation of the Endpoint*

Categories will be assigned to numeric values as follows: “Much better” = 1, “A little better” = 2, “No change” = 3, “A little worse” = 4, and “Much worse” = 5.

- *Analysis of the Endpoint*

The number and of percentage of subjects in each category (“Much better”, “A little better”, “No change”, “A little worse”, “Much worse”) in PGI-C daily impacts will be summarized descriptively by treatment group for subjects in the FAS.

Additionally, as a key secondary efficacy analysis, the average response in PGI-C daily impacts scale, using the assigned numeric values of 1-5, will be compared between treatment groups at Day 90. An ANCOVA model, adjusting for the subject’s baseline PGI-S daily impacts scale category as a quantitative covariate using the assigned numeric values of 1-5, will be used. Subjects with missing data at Day 90 will be excluded from analysis.

7.6. Pure Tone Audiometry

Standard Pure Tone Audiometry will be measured to determine a subject’s threshold for hearing at various frequencies and will be performed at the Screening/Start of Lead-In, Lead-In, End of Lead-In/Treatment, Day 30, Day 60, Day 90, Day 180, and Day 270 visits. This will be performed on a calibrated audiometer by a licensed audiologist. The following frequencies will be obtained: Air: 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz; Bone: 0.5, 1, 2, 3, and 4 kHz. If both masked and unmasked results are available for the same visit, date, ear, and frequency, the masked results will be used for analysis.

Post-Screening PTA thresholds with missing response values, specifically, no response due to a subject's audiometric threshold greater than the maximum calibrated dB of the equipment at a given frequency, will be imputed using the maximum dB for the audiometry equipment plus 5 dB. The value, maximum dB for the audiometry equipment plus 5 dB, was collected on the CRF as audiometer upper limit and the result will be classified as no signal at that frequency. Missing response values at Screening will not be imputed and remain missing.

Pure tone audiometry results will be presented in a data listing for the FAS.

7.6.1. Air and Bone Conduction audiometry dB HL thresholds by frequency

- *Computation of the Endpoint*

At each visit and by ear (left, right), the AC and BC audiometry dB HL thresholds will be recorded for each frequency (Air: 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz; Bone: 0.5, 1, 2, 3, and 4 kHz). Left and right ears will be mapped to treated and untreated for analysis. Missing values will be imputed per Section 7.6.

- *Analysis of the Endpoint*

Separately for AC and BC, the hearing threshold at each frequency will be summarized descriptively for treated and untreated ears separately by visit and treatment group for subjects in the FAS.

A line plot of the mean AC audiometry thresholds by frequency will be prepared for treated and untreated ears for each treatment group with lines connecting each point.

7.6.2. Mean overall PTA (AC over 0.5, 1, 2, and 4 kHz) and BCA (BC over 0.5, 1, 2 and 4 kHz)

- *Computation of the Endpoint*

At each visit and by ear (left, right), the mean overall PTA will be derived by averaging the AC audiometry dB HL thresholds over 0.5, 1, 2, and 4 kHz frequencies. Left and right ears will be mapped to treated and untreated for analysis. Missing values will be imputed per Section 7.6. The BCA will be derived using the same approach. If hearing thresholds are missing for any of the 0.5, 1, 2, and 4 kHz frequencies (after imputation of records with classification of "NR"), PTA or BCA will be missing, respectively.

- *Analysis of the Endpoint*

The mean overall PTA will be summarized descriptively for treated ears by visit and treatment group for subjects in the FAS. The summary will be repeated for BCA.

7.6.3. AC and BC improvement ≥10 and ≥15 dB HL from baseline, separately, for two contiguous frequencies

- *Computation of the Endpoint*

AC improvement ≥10 dB HL from baseline for two contiguous frequencies at each post-baseline visit for treated ears will be computed as 1 if the post-baseline threshold – baseline threshold is ≥10 dB HL for two contiguous frequencies and as 0, otherwise. The endpoint will utilize imputed values per Section 7.6. The AC improvement ≥15 dB HL, BC improvement ≥10 dB HL, and BC improvement ≥15 dB HL will be derived using the same approach.

- *Analysis of the Endpoint*

The incidence of AC improvement ≥10 dB HL from baseline for two contiguous frequencies at each post-baseline visit for treated ears will be summarized using frequencies and percentages by visit and treatment group for subjects in the FAS. The summary will be repeated for ≥15 dB HL and for BC improvement, ≥10 and ≥15 dB HL.

7.6.4. AC and BC improvement ≥15 and ≥20 dB HL from baseline, separately, for any frequency

- *Computation of the Endpoint*

AC improvement ≥15 dB HL from baseline for any frequency at each post-baseline visit for treated ears will be computed as 1 if the post-baseline threshold – baseline threshold is ≥15 dB HL for any frequency and as 0, otherwise. The endpoint will utilize imputed values per Section 7.6. The AC improvement ≥ 20 dB HL, BC improvement ≥15 dB HL, and BC improvement ≥20 dB HL will be derived using the same approach.

- *Analysis of the Endpoint*

The incidence of AC improvement ≥15 dB HL from baseline for any frequency at each post-baseline visit for treated ears will be summarized using frequencies and percentages by visit and treatment group for subjects in the FAS. The summary will be repeated for ≥20 dB HL and for BC improvement, ≥15 dB HL and ≥20 dB HL.

7.6.5. AC and BC composite improvement from baseline

- *Computation of the Endpoint*

The first AC composite improvement endpoint is defined as the occurrence of either or both of the following conditions for a given subject's ear for a given visit: 1) AC improvement ≥10 dB HL from baseline for two contiguous frequencies as described in Section 7.6.2 or 2) AC improvement ≥15 dB HL from baseline for any frequency as defined in Section 7.6.4. The first BC composite improvement endpoint is defined using the same approach.

The second AC composite improvement endpoint is defined as the occurrence of either or both of the following conditions for a given subject's ear for a given visit: 1) AC

improvement ≥15 dB HL from baseline for two contiguous frequencies as described in Section 7.6.2 or 2) AC improvement ≥20 dB HL from baseline for any frequency as defined in Section 7.6.4. The second BC composite improvement endpoint is defined using the same approach.

- *Analysis of the Endpoint*

The incidence of each AC composite improvement endpoint at each post-baseline visit for treated ears will be summarized using frequencies and percentages by visit and treatment group for subjects in the FAS. The summary will be repeated for each BC composite improvement endpoints.

In treated ears only for subjects in the FAS, post-baseline treatment group comparisons through day 90 for the incidence of AC composite improvement from baseline may be analyzed using a GEE model. With the binomial distribution assumption and logit link, the model will include fixed effects of treatment group, visit, interaction between visit and treatment group, baseline mean overall PTA, interaction between baseline mean overall PTA and visit, and randomization stratification factors. If the model fails to converge, the randomization stratification factors will be excluded from the model. The odds ratios along with 95% CIs and p-values between treatment groups will be reported by post-baseline visit. The analysis may be repeated for the incidence of BC composite improvement using a similar approach replacing the baseline mean overall PTA with the baseline mean overall BCA.

7.6.6. Change from baseline in Mean overall PTA and BCA

- *Computation of the Endpoint*

Using the mean overall PTA from Section 7.6.2, change from baseline in PTA will be computed as w – b where "w" is the post-baseline PTA and "b" is the PTA at baseline for each visit by ear (left, right). Left and right ears will be mapped to treated and untreated for analysis. The change from baseline in BCA will be derived using the same approach.

- *Analysis of the Endpoint*

The change from baseline in mean overall PTA will be summarized descriptively for treated ears by visit and treatment group for subjects in the FAS. The summary will be repeated for BCA.

7.6.7. Shifts from baseline in Mean overall PTA Categories

- *Computation of the Endpoint*

Mean overall PTA for each ear will be categorized into <26, 26-40, 41-55, 56-70, and >70 for each visit and shifts from baseline to each post-baseline visit will be computed (e.g., 26-40 to 41-55).

- *Analysis of the Endpoint*

The distribution in the shift in mean overall PTA categories for treated ears from baseline to each post-baseline visit will be summarized using frequencies and percentages by visit and treatment group for subjects in the FAS.

7.6.8. Mean low AC dB HL threshold (AC over 0.25, 0.5, 1, and 2 kHz)

- *Computation of the Endpoint*

At each visit and by ear (left, right), the mean low AC dB HL threshold will be derived by averaging the AC audiometry dB HL thresholds over 0.25, 0.5, 1, and 2 kHz frequencies. Left and right ears will be mapped to treated and untreated for analysis. Missing values will be imputed per Section 7.6.

- *Analysis of the Endpoint*

The mean low AC dB HL threshold will be summarized descriptively for treated ears by visit and treatment group for subjects in the FAS.

7.6.9. Mean high AC dB HL threshold (AC over 3, 4, 6 and 8 kHz)

- *Computation of the Endpoint*

At each visit and by ear (left, right), the mean high AC dB HL threshold will be derived by averaging the AC audiometry dB HL thresholds over 3, 4, 6 and 8 kHz frequencies. Left and right ears will be mapped to treated and untreated for analysis. Missing values will be imputed per Section 7.6.

- *Analysis of the Endpoint*

The mean high AC dB HL threshold will be summarized descriptively for treated ears by visit and treatment group for subjects in the FAS.

7.6.10. Air-Bone Imbalance at 0.5, 1, 2, 3, and 4 kHz

- *Computation of the Endpoint*

At each visit and by ear (left, right), Air-Bone imbalance is computed as AC-BC dB HL thresholds at 0.5, 1, 2, 3, and 4 kHz. Left and right ears will be mapped to treated and untreated for analysis. Missing threshold values will be imputed per Section 7.6 prior to the derivation.

- *Analysis of the Endpoint*

The Air-Bone imbalance at each frequency (0.5, 1, 2, 3, and 4 kHz) will be summarized descriptively for treated ears by visit and treatment group for subjects in the FAS.

7.6.11. Shift from baseline in Air-Bone Imbalance at 0.5, 1, 2, 3, and 4 kHz

- *Computation of the Endpoint*

Air-bone imbalance at each frequency will be categorized into ≤10 dB HL versus >10 dB HL for each visit and shifts from baseline to each post-baseline visit will be computed (e.g., ≤10 dB HL to >10 dB HL).

- *Analysis of the Endpoint*

The distribution in the shift in air-bone imbalance for treated ears at each frequency from baseline to each post-baseline visit will be summarized using frequencies and percentages by visit and treatment group for subjects in the FAS.

7.7. Extended High Frequency Audiometry

Extended high frequency audiometry will be performed to determine a subject's threshold for hearing at frequencies beyond those in standard pure tone audiometry at the Screening/Start of Lead-In, Lead-In, End of Lead-In/Treatment, Day 30, Day 60, Day 90, Day 180, and Day 270 visits. This will be performed on a calibrated audiometer by a licensed audiologist. The following frequencies will be obtained: Air: 9, 10, 11.2, 12.4, 14, and 16 kHz. Because some audiometers use center frequencies that vary by small amounts, sites should use the threshold at the closest listed center frequency (e.g., 11 kHz may be used for 11.2 kHz; 12.5 kHz may be used for 12.4 kHz). If both masked and unmasked results are available for the same visit, date, ear, and frequency, the masked results will be used for analysis.

Post-Screening PTA thresholds with missing response values, specifically, no response due to a subject's audiometric threshold greater than the maximum calibrated dB of the equipment at a given frequency, will be imputed using the maximum dB for the audiometry equipment plus 5 dB. The value, maximum dB for the audiometry equipment plus 5 dB, was collected on the CRF as audiometer upper limit and the result will be classified as no signal at that frequency. Missing response values at Screening will not be imputed and remain missing.

Extended high frequency audiometry results will be presented in a data listing for subjects in the FAS.

7.7.1. Air audiometry dB HL thresholds by frequency

- *Computation of the Endpoint*

At each visit and by ear (left, right), the AC audiometry dB HL thresholds will be recorded for each frequency (9, 10, 11.2, 12.4, 14, and 16 kHz). Left and right ears will be mapped to treated and untreated for analysis. Missing values will be imputed per Section 7.7.

- *Analysis of the Endpoint*

Descriptive summaries and the line plot will be performed for AC audiometry dB HL thresholds as described in Section 7.6.1.

7.7.2. Mean dB HL threshold (AC over 9-16 kHz)

- *Computation of the Endpoint*

At each visit and by ear (left, right), the mean dB HL threshold will be derived by averaging the AC audiometry dB HL thresholds over 9-16 kHz frequencies. Left and right ears will be mapped to treated and untreated for analysis. Missing values will be imputed per Section 7.7.

- *Analysis of the Endpoint*

The mean dB HL threshold will be summarized descriptively for treated ears by visit and treatment group for subjects in the FAS.

7.7.3. AC improvement ≥10 dB HL and ≥15 dB HL from baseline, separately, for two contiguous frequencies

- *Computation of the Endpoint*

AC improvement ≥10 dB HL from baseline for two contiguous frequencies at each post-baseline visit for treated ears will be computed as 1 if the post-baseline threshold – baseline threshold is ≥10 dB HL for two contiguous frequencies and as 0, otherwise. The endpoint will utilize imputed values per Section 7.7. The AC improvement ≥15 dB HL will be derived using the same approach.

- *Analysis of the Endpoint*

AC improvement ≥10 dB HL from baseline for two contiguous frequencies will be summarized using frequencies and percentages for treated ears by visit and treatment group for subjects in the FAS. The summary will be repeated for AC improvement ≥15 dB HL.

7.7.4. AC improvement ≥15 and ≥20 dB HL from baseline, separately, for any frequency

- *Computation of the Endpoint*

AC improvement ≥15 dB HL from baseline for any frequency at each post-baseline visit for treated ears will be computed as 1 if the post-baseline threshold – baseline threshold is ≥15 dB HL for any frequency and as 0, otherwise. The endpoint will utilize imputed values per Section 7.7. The AC improvement ≥20 dB HL will be derived using the same approach.

- *Analysis of the Endpoint*

AC improvement ≥15 dB HL from baseline for any frequency will be summarized using frequencies and percentages for treated ears by visit and treatment group for subjects in the FAS. The summary will be repeated for AC improvement ≥20 dB HL.

7.7.5. AC composite improvement from baseline

- *Computation of the Endpoint*

The first AC composite improvement endpoint is defined as the occurrence of either or both of the following conditions for a given subject's ear for a given visit: 1) AC improvement ≥10 dB HL from baseline for two contiguous frequencies as described in Section 7.7.3 or 2) AC improvement ≥15 dB HL from baseline for any frequency as defined in Section 7.7.4.

The second AC composite improvement endpoint is defined as the occurrence of either or both of the following conditions for a given subject's ear for a given visit: 1) AC improvement ≥15 dB HL from baseline for two contiguous frequencies as described in Section 7.7.3 or 2) AC improvement ≥20 dB HL from baseline for any frequency as defined in Section 7.7.4.

- *Analysis of the Endpoint*

The incidence of each AC composite improvement endpoint at each post-baseline visit for treated ears will be summarized using frequencies and percentages for treated ears by visit and treatment group for subjects in the FAS.

In treated ears only for subjects in the FAS, post-baseline treatment group comparisons through day 90 for incidence of AC composite improvement from baseline may be analyzed using a GEE model. With the binomial distribution assumption and logit link, the model will include fixed effects of treatment group, visit, interaction between visit and treatment group, baseline mean dB HL threshold (AC over 9-16 kHz), interaction between baseline mean dB HL threshold (AC over 9-16 kHz) and visit, and randomization stratification factors. If the model fails to converge, the randomization stratification factors will be excluded from the model. The odds ratios along with 95% CIs and p-values between treatment groups will be reported by post-baseline visit.

7.7.6. Shift from baseline of no signal to any signal by frequency

- *Computation of the Endpoint*

For each frequency, shifts from no signal to any signal will be computed in subjects in the FAS with no signal (missing/imputed hearing response) at baseline in the treated ear. At each post-baseline visit, subjects with any signal (any non-missing/not imputed hearing response) in the treated ear will be flagged as 1 and as 0, otherwise. The endpoint will utilize imputed values per Section 7.7.

- *Analysis of the Endpoint*

For each frequency, the incidence of shifts from no signal at baseline to any signal at each post-baseline visit for treated ears will be summarized using frequencies and percentages by visit and treatment group for subjects with no signal at baseline in the FAS.

7.7.7. Shift from baseline of no signal to any signal in two contiguous frequencies

- *Computation of the Endpoint*

Shifts from no signal in two contiguous frequencies at baseline to any signal in two contiguous frequencies at each post-baseline visit will be computed in subjects in the FAS with no signal (missing/imputed hearing response) at baseline in the treated ear for any two contiguous frequencies. At each post-baseline visit, subjects with any signal (any non-missing/not imputed hearing response) in the treated ear at the same two contiguous frequencies will be flagged as 1 and as 0, otherwise. The endpoint will utilize imputed values per Section 7.7.

- *Analysis of the Endpoint*

The incidence of shifts from no signal in two contiguous frequencies at baseline to any signal in two contiguous frequencies at each post-baseline visit for treated ears will be summarized using frequencies and percentages by visit and treatment group for subjects in the FAS with no signal in any two contiguous frequencies at baseline in the treated ear.

7.7.8. Shift from baseline of no signal to any signal in three contiguous frequencies

- *Computation of the Endpoint*

Shifts from no signal in three contiguous frequencies at baseline to any signal in three contiguous frequencies at each post-baseline visit will be computed in subjects in the FAS with no signal (missing/imputed hearing response) at baseline in the treated ear for any three contiguous frequencies. At each post-baseline visit, subjects with any signal (any non-missing/not imputed hearing response) in the treated ear in the same three contiguous frequencies will be flagged as 1 and as 0, otherwise. The endpoint will utilize imputed values per Section 7.7.

- *Analysis of the Endpoint*

The incidence of shifts from no signal in three contiguous frequencies at baseline to any signal in three contiguous frequencies at each post-baseline visit for treated ears will be summarized using frequencies and percentages by visit and treatment group for subjects in the FAS with no signal in three contiguous frequencies at baseline in the treated ear.

7.8. Examination of Subgroups

Non-stratified treatment differences between treatment groups in the incidence of WR Improvement at Day 90, as defined in section 7.3.1, for WR in Quiet improvement (Maryland CNC) in the FAS will be summarized within the subgroups listed below along with 95% CIs in a forest plot. Missing data will be imputed using LOCF. In the case a subgroup includes less than 20 subjects, the analysis for the given subgroup will not be carried out or combining subgroups may be considered.

- Subject Demographics

- Sex
- Race
- Ethnicity
- Age (18 to <35, 35 to <50, 50 to 65)

- Baseline Disease Characteristics
  - Duration of hearing loss (≤1, >1 to 5, >5 to 10, >10 years from screening)
  - Etiology of hearing loss
  - Individual randomization stratification factors:
    - Visit 2 (Day -15) Maryland CNC Word Recognition Score (above or equal to 28% words in quiet correct, below 28% words in quiet correct)
    - Hearing loss laterality (unilateral, bilateral)

8. SAFETY EVALUATION

8.1. Overview of Safety Analysis Methods

The assessment of safety of single dose of FX-322 or Placebo in subjects with acquired sensorineural hearing loss is an objective of this study. The safety analyses will be performed for the SfAS and will include treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), vital signs, physical examination, otoscopic examination, tympanometry, concomitant medications, and C-SSRS assessments. Tabular summaries of descriptive statistics will be presented for all subjects included in the SfAS and subjects will be classified into actual treatment groups. Where appropriate, the actual treated ear will be distinguished from the actual untreated ear.

Safety data will generally not be imputed, except for partial and missing dates, which will be imputed only for defining TEAEs and concomitant medications for analysis and reporting purposes. The detailed imputation rules are specified in section 8.3.1. Imputed dates will not be presented in data listings.

8.2. Extent of Exposure

Exposure will be summarized descriptively by actual treatment group and overall for subjects in the SfAS for the following parameters:

- Number and percentage of subjects receiving study treatment in the study ear
- Number and percentage of subjects with a full dose administered
- Number and percentage of subjects receiving incorrect study treatment in the study ear to be treated
- Number and percentage of subjects treated in the non-study ear

An exposure listing will be provided, including all available exposure data.

8.3. Adverse Events

All AEs will be recorded from the time of the treatment through the end of the observational period. Adverse events onset or worsening, on or after the study drug administration are considered TEAEs. TEAEs will be tabulated by treatment group for all subjects in the SfAS and will be flagged in the "all AEs" listing. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Any ear-related AE, whether occurring in 1 or both ears, will only be counted at most once in subject-level counts per system organ class (SOC) and preferred term (PT).

The following analyses will be conducted:

- Overall summary of TEAEs
- Overall summary of TEAEs by SOC and PT
- Overall summary of TEAEs presented by maximum severity (Mild, Moderate, or Severe), by SOC and PT
- Overall summary of TEAEs presented by maximum relationship (Related, Possible, Unlikely or Not Related) to study drug, by SOC and PT

For ear-related TEAE analyses where the ear is the unit of analysis, an event will be attributed its occurrence to either the treated ear, the untreated ear, or both ears. The ear-related TEAE analyses will be conducted by treatment group for the following:

- Overall summary of ear-related TEAEs presented by ear attribution, by SOC and PT
- Overall summary of ear-related TEAEs presented by ear attribution, by phase (up to Day 30, Day 30-90, and after Day 90), SOC and PT

8.3.1. Imputation Rules for Missing AE Date/Time of Onset/Resolution

Partial dates will be imputed for the purposes of defining TEAEs as follows:

- For a missing start day where the month and year are present, the start day will be set to the first day of the month, unless the following two conditions are met:

  1. the first day of the month is before the date of administration of study drug and the month and year are the same as the month and year of the date of administration of study drug, and

  2. the end date is on or after the date of administration of study drug or the end date is completely missing.

  If the two above conditions are met, the start day will be set to the day of administration of study drug.

- For a missing start day and month where the year is present, the start day and month will be set to January 1st, unless 1) January 1st is before the date of

administration of study drug and the year is the same as the year of the date of administration of study drug, and 2) the end date is on or after the date of administration of study drug or the end date is completely missing, in which case the start day and month will be set to that of the date of administration of study drug.

- For a missing end day where the month and year are present, the end day will be set to the last day of the month, unless the month and year are the same as the month and year of the last contact date for the subject, in which case the end day will be set to that of the subject's last contact date, which is captured in SDTM as DM.RFPENDTC (Date/Time of End of Participation) with derivation rule specified in the study SDTM specifications.

- For a missing end day and month where the year is present, the end day and month will be set to the subject's last contact date, unless the year of the subject's last contact date is greater than the end year, in which case the end day and month will be set to December 31st.

Completely missing dates will be imputed for the purposes of classifying TEAEs as follows:

- For an entirely missing start date (i.e., day, month, and year are missing), the start date will be set to the date of administration of study drug unless the end date is prior to the date of administration of study drug, in which case the start date will be set to the end date.

8.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events

Treatment-emergent SAEs, TEAEs leading to study withdrawal, and fatal TEAEs will be summarized for all subjects in the SfAS by treatment group for the following:

- Overall summary of SAE by SOC and PT
- Overall summary of TEAE leading to study withdrawal by SOC and PT
- Overall summary of fatal TEAE by SOC and PT

SAEs, adverse events leading to study withdrawal, and fatal AEs will be presented in data listings for subjects in the SfAS.

Adverse Events of Special Interest (AESI), defined in the Protocol, will be summarized by treatment group, SOC, and PT for all subjects in the SfAS. AESIs that occur after study treatment injection will be presented in a data listing for subjects in the SfAS.

8.5. Urine Pregnancy Tests

Urine pregnancy test results will be included in a listing for subjects in the SfAS.

8.6. Vital Signs, Physical Findings, and Other Observations Related to Safety

8.6.1. Vital Signs

Vital signs collected on the CRF will be provided in a listing for subjects in the SfAS. The number and percentage of subjects with clinically notable vital signs as defined below will be summarized for post-baseline visits by treatment group for subjects in the SfAS.

- Systolic blood pressure (BP)
  - ≥180 mmHg and an increase ≥20 mmHg from baseline
  - ≤90 mmHg and a decrease ≥20 mmHg from baseline
- Diastolic BP
  - ≥105 mmHg and an increase ≥15 mmHg from baseline
  - ≤50 mmHg and a decrease ≥15 mmHg from baseline
- Heart rate
  - ≥120 bpm with an increase from baseline of ≥15 bpm
  - ≤50 bpm with a decrease from baseline of ≥15 bpm
- Temperature
  - >38 ^{o}C
  - <35 ^{o}C

Unscheduled visit and early termination visit data will not be mapped to scheduled visits per Section 7.1.2. Unscheduled visit and early termination visit data will be excluded from summary tables and included in listings.

8.6.2. Physical Examinations

Physical examination results of Normal, Abnormal and Not Done will be included in listings for subjects in the SfAS.

8.6.3. Otoscopic Examinations

Otoscopic examinations including external inspection and internal ear examination, will be performed at the Screening/Start of Lead-In, End of Lead-In/Treatment, Day 30, Day 60, Day 90, Day 180, and Day 270 visits. Otoscopic examination data will be summarized descriptively by visit for treated ears by treatment group for subjects in the SfAS. An otoscopic findings shift table for treated ears from baseline to post-baseline visits will also be produced by treatment group. Unscheduled visit and early termination visit data will not be mapped to scheduled visits per Section 7.1.2. Unscheduled visit and early termination visit data will be excluded from summary tables and included in listings.

Otoscopic examination data for both treated and untreated ears, scheduled and unscheduled, will be presented in a data listing for subjects in the SfAS.

8.6.4. Tympanometry

Tympanometry will be performed at the Screening/Start of Lead-In, End of Lead-In/Treatment, Day 30, Day 60, Day 90, Day 180, and Day 270 visits. Tympanometry data including type of tympanogram, ear canal volume, peak admittance, and peak pressure will be summarized descriptively for treated ears by visit and treatment group for subjects in the SfAS. A tympanogram classification shift table for treated ears from baseline to post-baseline visits will also be produced by treatment group. Unscheduled visit and early termination visit data will not be mapped to scheduled visits per Section 7.1.2. Unscheduled visit and early termination visit data will be excluded from summary tables and included in listings.

All tympanogram data for both treated and untreated ears, scheduled and unscheduled, will be presented in a data listing for subjects in the SfAS.

8.6.5. Columbia-Suicide Severity Rating Scale Assessments

The C-SSRS will be completed at the End of Lead-In/Treatment (Baseline/Screening version), Day 30, Day 60, Day 90, Day 180, and Day 270 visits. All suicidal ideation and behavioral variables collected will be summarized descriptively for each visit by treatment group for subjects in the SfAS.

All C-SSRS data, scheduled and unscheduled, will be included in data listings for all subjects in the SfAS.

8.6.6. Concomitant Medications

All medications taken within 14 days prior to the Screening/Start of Lead-In visit through the end of the follow-up period will be recorded on the Concomitant Medications log. Prior and concomitant medications will be coded using World Health Organization Drug Dictionary Enhanced.

Concomitant medications will include all non-trial medications that are taken on or after administration of study drug. Prior medications will include all non-trial medications that are started prior to the day of administration of the study drug.

The number and percentage of subjects using concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) and PT for all subjects in the SfAS by treatment group. For subject-level analysis, a subject will be counted at most once per ATC and per PT.

Prior and concomitant medication data will also be presented in a data listing for subjects in the SfAS.

8.6.6.1. Imputation Rules for Missing Concomitant Medication Start/Stop Date

Partial and completely missing dates will be imputed for the purposes of classifying concomitant medications as follows:

- Partial dates will be imputed following the same algorithm as for TEAEs.
- For an entirely missing start date (i.e., day, month, and year are missing), the start date will be set to the date of administration of study drug unless the stop date is prior to the date of administration of study drug, in which case the start date will be set to the stop date.

9. OTHER ANALYSES

9.1. [redacted] Qualitative Questionnaire

This questionnaire records subject experience [redacted]

9.1.1. Qualitative questionnaire responses

- *Analysis of the Endpoint*

Responses to the [redacted] questionnaire will be summarized with frequencies and percentages by item for subjects in the SfAS.

9.2. Tinnitus Functional Index

The Tinnitus Functional Index (Meikle et al 2012) has eight subscales that address the intrusiveness of tinnitus, the sense of control the patient has, cognitive interference, sleep disturbance, auditory issues, relaxation issues, quality of life, and emotional distress. The subject will report answers to each of the 25 questions using a scale of 0-10. The TFI will be given to the subject to complete at the End of Lead-In/Treatment, Day 90, Day 180, and Day 270 visits.

All instrument items, except items 1 and 3, are on an inverted 0-10 scale with 0 being most favorable and 10 being least favorable. Items 1 and 3 are on an inverted 0% to 100% scale with 0% being most favorable and 100% being least favorable. The total score and individual subscale scores are the average item response (all subscales consist of 3 or 4 items) that is then scaled to 0-100. Detailed scoring instructions are in Section 14.3.

No imputation will be performed for missing data and Section 14.3 provides further detail regarding the impact of missing data on TFI scores. No sensitivity analyses will be performed for the TFI endpoints.

9.2.1. Mean total score, individual subscale scores, and loudness score

- *Computation of the Endpoint*

At each visit, the mean total TFI score and individual subscale scores will be computed per Section 14.3. The loudness score will be the response from item 2.

- *Analysis of the Endpoint*

The mean total TFI score, individual subscale scores, and loudness score will be summarized descriptively by visit and treatment group for subjects in the FAS.

9.2.2. Change from baseline in mean total score, individual subscale scores, and loudness score

- *Computation of the Endpoint*

The change from baseline to each post-baseline visit will be computed as w – b where "w" is the post-baseline score and "b" is the score at baseline.

- *Analysis of the Endpoint*

The change from baseline to each post-baseline visit in mean total TFI score, individual subscale scores, and loudness score will be summarized descriptively by visit and treatment group for subjects in the FAS.

9.3. Research Assessment on [redacted] Quality of Life [redacted]

[redacted] is a [redacted] PRO questionnaire [redacted] The subject will complete the instrument at the End of Lead-In/Treatment and Day 90 visits.

[redacted]

9.3.1. Mean total score, mean domain scores, and individual scores

- *Computation of the Endpoint*

At each visit, the mean [redacted] score and mean domain scores will be computed per [redacted] No computation is required for individual scores.

- *Analysis of the Endpoint*

The mean [redacted] score, mean domain scores, and individual scores will be summarized descriptively by visit and treatment group for subjects in the FAS.

9.3.2. Change from baseline in mean total score, mean domain scores, and individual scores

- *Computation of the Endpoint*

[redacted]

Using the mean [redacted] score, mean domain scores, and individual scores [redacted]

- *Analysis of the Endpoint*

The change from baseline to each post-baseline visit in [redacted] score, mean domain scores, and individual scores will be summarized descriptively by visit and treatment group for subjects in the FAS.

9.3.3. Domain level compliance

- *Analysis of the Endpoint*

[redacted]

- [redacted]
- [redacted]
- [redacted]

9.4. Speech Reception Threshold (SRT)

Speech reception threshold is being used as a cross-check measure for the results of pure-tone audiometry. The PTA shall be compared to the SRT to alert the tester to possible concerns about the accuracy of the pure tone results. Left and right ears will be mapped to treated and untreated for analysis.

The qualitative assessment for whether the SRT results suggest hearing thresholds are reliable will be summarized descriptively for treated and untreated ears, separately, for subjects in the SfAS. All data, including the SRT value, will be listed for subjects in the SfAS.

10. INTERIM ANALYSIS AND DATA MONITORING

The blinded data will be continuously monitored for safety throughout the study. No interim analysis is planned.

11. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

Not applicable.

12. REFERENCES

Carney, E., & Schlauch, R. S. (2007). Critical Difference Table for Word Recognition Testing Derived Using Computer Simulation. Journal of Speech, Language, and Hearing Research, 50(5), 1203-1209.

Causey, G. D., Hood, L. J., Hermanson, C. L., & Bowling, L. S. (1984). The Maryland CNC test: normative studies. *Audiology*, *23*(6), 552-568.

DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. Controlled Clinical Trials, 7, 177-188.

FDA (2020). Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency. Guidance for Industry. Published June 2020. Available from: https://www.fda.gov/media/139145/download.

Studebaker, G. A. (1985). A "rationalized" arcsine transform. Journal of Speech, Language, and Hearing Research, 28(3), 455-462.

Thornton, A. R., & Raffin, M. J. (1978). Speech-discrimination scores modeled as a binomial variable. Journal of speech and hearing research, 21(3), 507-518.

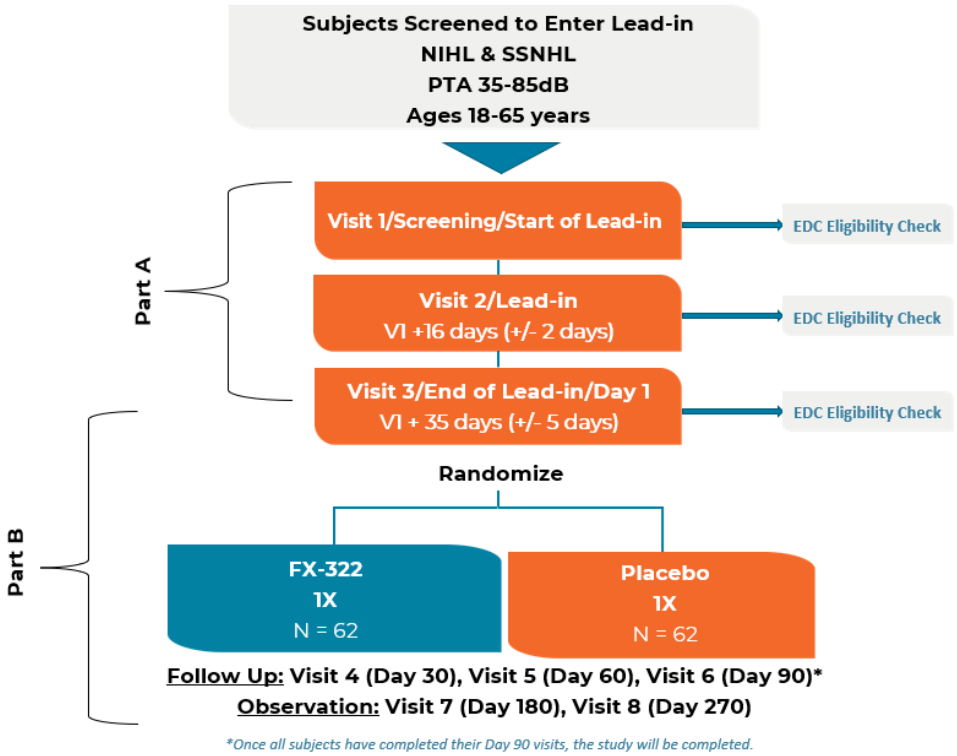
Wilson, R. H., Morgan, D. E., & Dirks, D. D. (1973). A proposed SRT procedure and its statistical precedent. Journal of Speech and Hearing Disorders, 38(2), 184-191.

Wilson RH, Abrams, HB, Pillion AL. (2003). A word-recognition task in multitalker babble using a descending presentation mode from 24 dB to 0 dB signal to babble. J Rehabil Res Dev. 2003 Jul-Aug; 40(4):321-7.

[redacted]

13. APPENDICES

13.1. Study Flow Chart



13.2. Schedule of Assessments

Visit	Screening/ Start of Lead-In	Lead-In Visit	End of Lead-In/ Treatment	In-Clinic Follow-up	In-Clinic Follow up	In-Clinic Follow-up / ET[e]	In-Clinic Observation	In-Clinic Observation	Un-scheduled Visit
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**UNS**
Assessment/Day	**Day -40 to -30**	**Visit 1 + 16 days**	**Visit 1 + 35 days**	**Day 30**	**Day 60**	**Day 90**	**Day 180**	**Day 270**	
Visit Window	**N/A**	**+/- 2 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 7 days**	**+/- 7 days**	**N/A**
Informed Consent	X								
Inclusion/ Exclusion Criteria	X[a]	X[a]	X[b]						
Eligibility Assessment by EDC	X	X	X[b]						
Demographics	X[a]								
Medical History	X[a]	X[a]	X[b]						
Concomitant Medication	X[a]	X[a]	X[b, c]	X	X	X	X	X	X
Physical Examination including weight and height	X								X[d]
Vital Signs (body temperature, pulse rate, bp)	X	X	X[b]	X	X	X			X[d]
Tympanometry	X		X[b]	X	X	X	X	X	X[d]
Standard Pure Tone Audiometry	X	X	X[b]	X	X	X	X	X	X[d]
Speech Reception Threshold (SRT)	X	X	X	X	X	X	X	X	X[d]
Extended High Frequency Audiometry	X	X	X[b]	X	X	X	X	X	X[d]
Word recognition, quiet (Maryland CNC)	X	X	X[b]	X	X	X	X	X	X[d]
Word recognition (W-22)	X	X	X[b]	X	X	X	X	X	X[d]
Words in noise (WIN)	X	X	X[b]	X	X	X	X	X	X[d]
Tinnitus Functional Index			X[b]			X	X	X	X[d]
[redacted]	[redacted]								

[redacted]

Visit	Screening/ Start of Lead-In	Lead-In Visit	End of Lead-In/ Treatment	In-Clinic Follow-up	In-Clinic Follow up	In-Clinic Follow-up / ET[e]	In-Clinic Observation	In-Clinic Observation	Un-scheduled Visit
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**UNS**
Assessment/Day	**Day -40 to -30**	**Visit 1 + 16 days**	**Visit 1 + 35 days**	**Day 30**	**Day 60**	**Day 90**	**Day 180**	**Day 270**	
Visit Window	**N/A**	**+/- 2 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 7 days**	**+/- 7 days**	**N/A**
[redacted] Qualitative Questionnaire	[redacted]								
Columbia Suicide Severity Rating Scale			X[b]	X	X	X	X	X	X[d]
PGI-S Hearing Loss Scale			X[b]						
PGI-S Daily Impacts Scale			X[b]						
PGI-C Hearing Loss Scale						X			
PGI-C Daily Impacts Scale						X			
Otoscopy	X		X[b]	X	X	X	X	X	X[d]
Urine Pregnancy Test (women of childbearing potential only)	X		X[b]			X			X[d]
Randomization by EDC			X[b]						
Study Medication (FX-322 or placebo)			X						
Adverse Events			X[c]	X	X	X	X	X	X

a- Performed during the Screening Visit and again if a subject notes a change in their medical status during the lead in period
b – Assessment performed prior to injection
c- Assessments performed after injection
d- Perform at Investigator Discretion
e- If a subject discontinues prior to Visit 6 (Day 90), all efforts should be made to complete the Visit 6 (Day 90) In-Clinic Follow-up/Early Termination (ET) Visit as soon as possible and, whenever possible, prior to starting any new medication or treatment.

14. ATTACHMENTS

14.1. Thornton and Raffin (1978) Word Recognition Scoring Chart

TABLE 4. Lower and upper limits of the 95% critical differences for percentage scores. Values within the range shown are not significantly different from the value shown in the percentage Score columns ($p > 0.05$).

% Score	n = 50	n = 25	n = 10	% Score	n = 100*
0	0-4	0-8	0-20	50	37-63
2	0-10			51	38-64
4	0-14	0-20		52	39-65
6	2-18			53	40-66
8	2-22	0-28		54	41-67
10	2-24		0-50	55	42-68
12	4-26	4-32		56	43-69
14	4-30			57	44-70
16	6-32	4-40		58	45-71
18	6-34			59	46-72
20	8-36	4-44	0-60	60	47-73
22	8-40			61	48-74
24	10-42	8-48		62	49-74
26	12-44			63	50-75
28	14-46	8-52		64	51-76
30	14-48		10-70	65	52-77
32	16-50	12-56		66	53-78
34	18-52			67	54-79
36	20-54	16-60		68	55-80
38	22-56			69	56-81
40	22-58	16-64	10-80	70	57-81
42	24-60			71	58-82
44	26-62	20-68		72	59-83
46	28-64			73	60-84
48	30-66	24-72		74	61-85
50	32-68		10-90	75	63-86
52	34-70	28-76		76	64-86
54	36-72			77	65-87
56	38-74	32-80		78	66-88
58	40-76			79	67-89
60	42-78	36-84	20-90	80	68-89
62	44-78			81	69-90
64	46-80	40-84		82	71-91
66	48-82			83	72-92
68	50-84	44-88		84	73-92
70	52-86		30-90	85	74-93
72	54-86	48-92		86	75-94
74	56-88			87	77-94
76	58-90	52-92		88	78-95
78	60-92			89	79-96
80	64-92	56-96	40-100	90	81-96
82	66-94			91	82-97
84	68-94	60-96		92	83-98
86	70-96			93	85-98
88	74-96	68-96		94	86-99
90	76-98		50-100	95	88-99
92	78-98	72-100		96	89-99
94	82-98			97	91-100
96	86-100	80-100		98	92-100
98	90-100			99	94-100
100	96-100	92-100	80-100	100	97-100

*If score is less than 50%, find % Score = 100-observed score and subtract each critical difference limit from 100.

14.2. Carney-Schlauch (2007) Word Recognition Scoring Chart

Table 1. Limits (upper and lower) of 95% critical differences for percent scores on lists of length n = 10, 25, 50, and 100.

% score	n = 50	n = 25	n = 10	% score	n = 100	% score	n = 100
0	0–6	0–12	0–20	50	37–63	50	37–63
2	0–10			49	36–62	51	38–64
4	0–14	0–20		48	35–61	52	39–65
6	0–18			47	34–60	53	40–66
8	2–**20**	0–28		46	33–59	54	41–67
10	2–24		0–**40**	45	32–58	55	42–68
12	4–26	0–32		44	31–57	56	43–69
14	4–**28**			43	30–56	57	44–70
16	6–32	4–40		42	29–55	58	45–71
18	6–34			41	28–54	59	46–72
20	8–36	4–44	0–**50**	40	**28**–53	60	47–**72**
22	**10**–**38**			39	**27**–52	61	48–**73**
24	10–42	8–48		38	26–51	62	49–74
26	12–44			37	25–50	63	50–75
28	14–46	8–52		36	24–49	64	51–76
30	**16**–48		10–70	35	23–48	65	52–77
32	16–50	12–56		34	22–47	66	53–78
34	18–52			33	23–46	67	54–79
36	20–54	16–60		32	20–45	68	55–80
38	22–56			31	**20**–44	69	56–**80**
40	**24**–58	16–64	10–**70**	30	19–43	70	57–81
42	24–60			29	18–42	71	58–82
44	26–62	20–68		28	17–41	72	59–83
46	28–64			27	16–**39**	73	**61**–84
48	30–66	24–72		26	15–**38**	74	**62**–85
50	32–68		**20**–**80**	25	**15**–37	75	63–**85**
52	34–70	28–76		24	14–36	76	64–86
54	36–72			23	13–35	77	65–87
56	38–74	32–80		22	12–34	78	66–88
58	40–76			21	11–31	79	69–89
60	42–**76**	36–84	**30**–90	20	11–32	80	68–89
62	44–78			19	10–**30**	81	**70**–90
64	46–80	40–84		18	9–29	82	71–91
66	48–82			17	8–28	83	72–92
68	50–84	44–88		16	8–27	84	73–92
70	52–**84**		30–90	15	7–26	85	74–93
72	54–86	48–92		14	6–**24**	86	**76**–94
74	56–88			13	6–23	87	77–94
76	58–90	52–92		12	5–22	88	78–95
78	**62**–**90**			11	4–21	89	79–96
80	64–92	56–96	**50**–100	10	4–19	90	81–96
82	66–94			9	3–18	91	82–97
84	68–94	60–96		8	**3**–17	92	83–**97**
86	**72**–96			7	2–15	93	85–98
88	74–96	68–100		6	1–14	94	86–99
90	76–98		**60**–100	5	1–12	95	88–99
92	**80**–98	72–100		4	1–11	96	89–99
94	82–100			3	0–9	97	91–100
96	86–100	80–100		2	0–**7**	98	**93**–100
98	90–100			1	0–6	99	94–100
100	94–100	88–100	80–100	0	0–3	100	97–100

Note. The upper and lower scores in the 95% critical interval are shown for various list sizes. Scores on successive administrations of a word recognition test may be considered to be "significantly different," at the .05 level, if they exceed the upper limit or fall below the lower limit. Discrepancies between these simulated values and those in Thornton and Raffin (1978) are coded as follows: numerals in boldface indicate that the critical interval is narrower on that side than in the previous table; underlined numerals indicate that the critical interval is wider on that side than in the previous table.

14.3. TFI Calculations

TINNITUS FUNCTIONAL INDEX

Today's Date _____ Your Name _____
Month / Day / Year *Please Print*

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

I **Over the PAST WEEK...**

1. What percentage of your time awake were you consciously **AWARE OF** your tinnitus?
Never aware ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◄ *Always aware*

2. How **STRONG** or **LOUD** was your tinnitus?
Not at all strong or loud ►0 1 2 3 4 5 6 7 8 9 10 ◄ *Extremely strong or loud*

3. What percentage of your time awake were you **ANNOYED** by your tinnitus?
None of the time ► 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% ◄ *All of the time*

SC **Over the PAST WEEK...**

4. Did you feel **IN CONTROL** in regard to your tinnitus?
Very much in control ►0 1 2 3 4 5 6 7 8 9 10 ◄ *Never in control*

5. How easy was it for you to **COPE** with your tinnitus?
Very easy to cope ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Impossible to cope*

6. How easy was it for you to **IGNORE** your tinnitus?
Very easy to ignore ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Impossible to ignore*

C **Over the PAST WEEK, how much did your tinnitus interfere with...**

7. Your ability to **CONCENTRATE**?
Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

8. Your ability to **THINK CLEARLY?**
Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

9. Your ability to **FOCUS ATTENTION** on other things besides your tinnitus?
Did not interfere ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Completely interfered*

SL **Over the PAST WEEK...**

10. How often did your tinnitus make it difficult to **FALL ASLEEP** or **STAY ASLEEP**?
Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

11. How often did your tinnitus cause you difficulty in getting **AS MUCH SLEEP** as you needed?
Never had difficulty ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *Always had difficulty*

12. How much of the time did your tinnitus keep you from **SLEEPING** as **DEEPLY** or as **PEACEFULLY** as you would have liked?
None of the time ► 0 1 2 3 4 5 6 7 8 9 10 ◄ *All of the time*

TINNITUS FUNCTIONAL INDEX PAGE 2

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

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

[redacted]

The possible responses to items except 1 and 3 are 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10. The possible responses to items 1 and 3 are 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100%. Prior to computing the TFI total score, the responses for items 1 and 3 are transformed from a percentage scale to a 0 to 10 scale, by dividing the values by 10.

The TFI total score is then defined as a sum of the 25 items, after items 1 and 3 are transformed. The total TFI score is calculated as the sum of the 25 scores, divided by the number of non-missing scores, multiplied by 10. The total score ranges from 0 to 100, with higher scores representing greater perceived handicap.

The TFI total score is not valid if 7 or more items are omitted. To be valid as a measure of tinnitus severity, at least 19 items must be completed.

TFI Subscales

The 25 items can also be grouped into 8 subscales: intrusive, sense of control, cognitive, sleep, auditory, relaxation, quality of life, and emotional.

- The intrusive group includes items 1, 2, and 3.
- The sense of control group includes items 4, 5, and 6.
- The cognitive group includes items 7, 8, and 9.
- The sleep group includes items 10, 11, and 12.
- The auditory group includes items 13, 14, and 15.
- The relaxation group includes items 16, 17, and 18.
- The quality of life group includes items 19, 20, 21, and 22.
- The emotional group includes items 23, 24, and 25.

The subscale scores will be computed by summing the points for each question included in the relevant subscale, dividing by the number of non-missing scores within the subscale, multiplied by 10. Each subscale score has a range of 0 to 100. Each TFI subscale score is not valid if 2 or more items are omitted. To be valid subscale scores, no more than 1 item can be omitted.

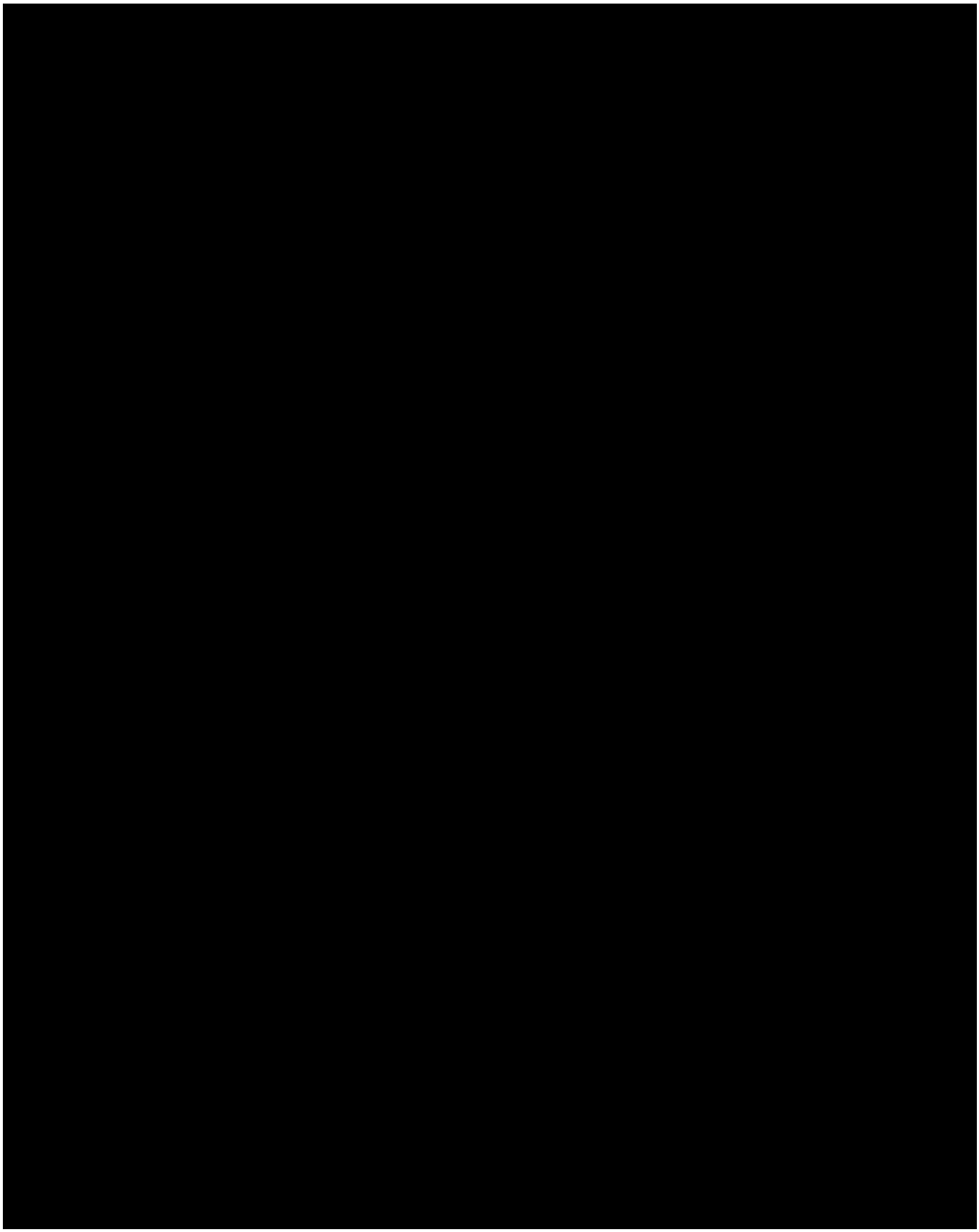
14.4. [redacted] Calculations

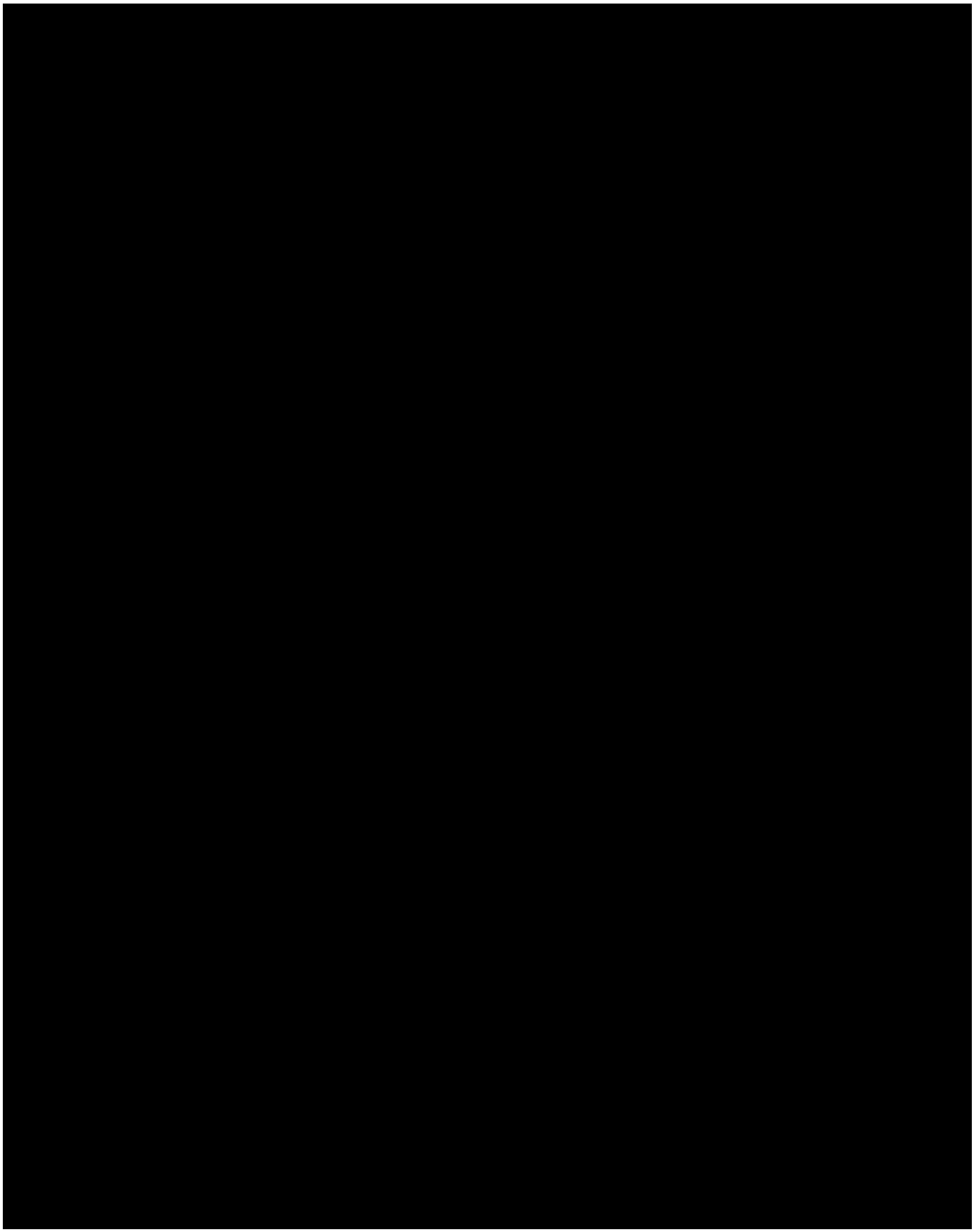
Research Assessment on [redacted] Quality of Life [redacted]

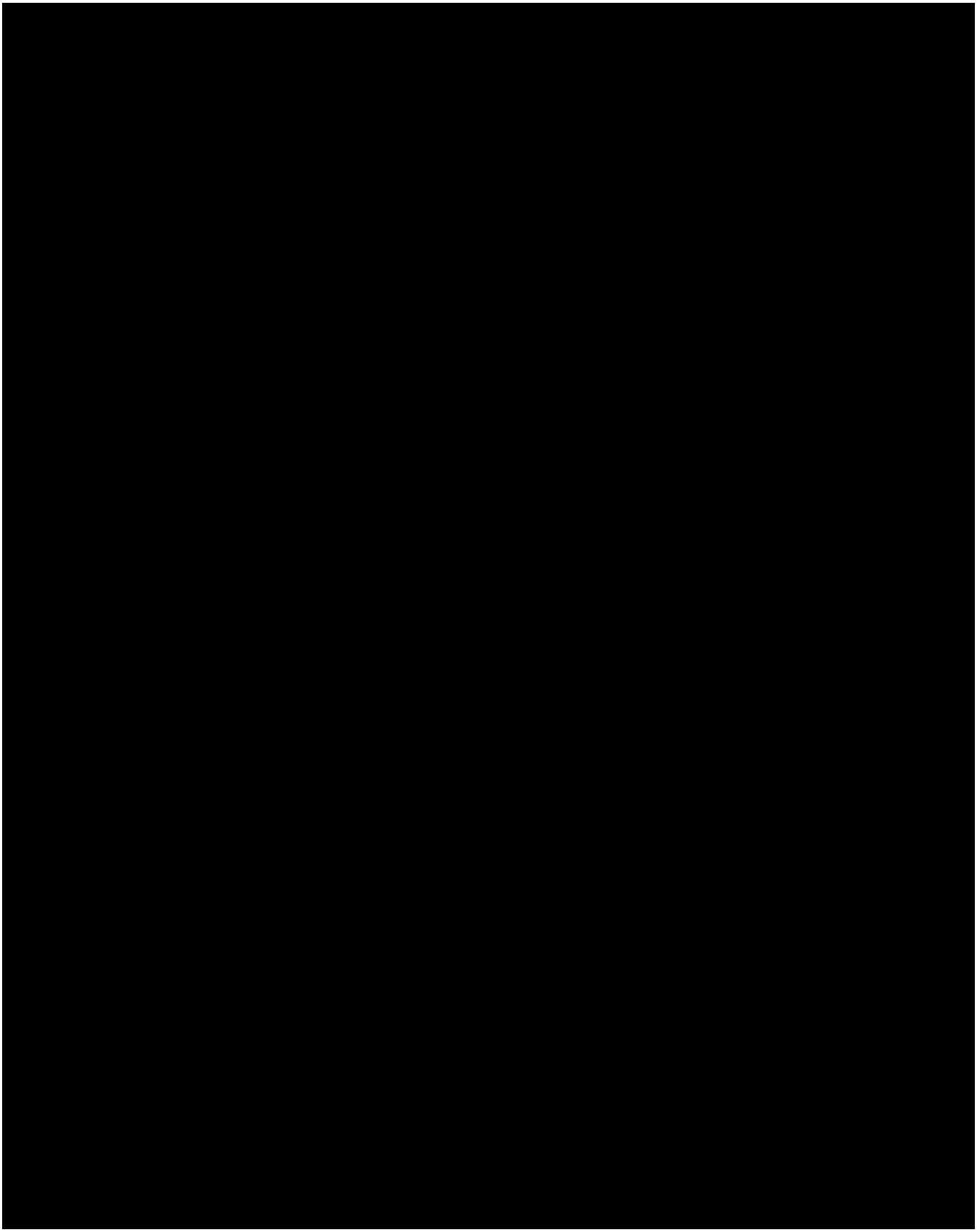
[redacted]

[redacted]

[redacted]







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