Statistical Analysis Plan

A Phase 1/2 Randomized, Double-blind, Placebo-controlled Single Dose Study at Two Dose Levels of FX-322 Administered by Intratympanic Injection in Adults with Stable Sensorineural Hearing Loss

Protocol Number: *FX-322-201*

Version *1.0*

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Previous Versions

Version 0.1, Issued: 08-Jun-2018

Version 0.2, Issued: 22-Jun-2018

Version 0.3, Issued: 23-Jul-2018

SAP Amendments before database lock

Version	Issue Date	Section	Revision/Addition	Rationale
	Not Applicable			

Table of Contents

1 INTRODUCTION

This document details the planned statistical analyses for the Frequency Therapeutics, protocol "FX-322-201" study titled "A Phase 1/2 Randomized, Double-blind, Placebo-controlled Single Dose Study at Two Dose Levels of FX-322 Administered by Intratympanic Injection in Adults with Stable Sensorineural Hearing Loss".

The proposed analyses are based on the amended version of the Protocol version 2.0 (dated 29-May-2018).

This is a Phase 1/2 randomized, double-blind, placebo-controlled, single dose study at two dose levels of FX-322 compared to placebo in adults with stable sensorineural hearing loss (no changes over six months of 10 dB or more in any frequency). The two dose levels proposed in this study, FX-322L and FX-322H will be dosed concurrently. The study will have three phases: Screening, Treatment with Observation, and Follow-up.

2 STUDY OBJECTIVES

The primary objectives of the study are:

- To assess the systemic safety of FX-322
- To assess the plasma pharmacokinetic (PK) profile to determine the systemic exposure to the active pharmaceutical ingredients
- To assess the effect of FX-322 on otologic and audiologic measures

3 ENDPOINTS

3.1 Safety Endpoints

The following safety assessments will be evaluated at the Screening visit and throughout: Treatment emergent adverse events (TEAEs), clinical laboratory tests (including hematology, serum chemistry, coagulation, and urinalysis), vital signs, physical examination, electrocardiogram (ECG), medical history, prior and concomitant medications, audiometry, and otoscopy.

3.2 Pharmacokinetic Endpoints

Serial blood samples will be collected predose and postdose through 24 hours to determine concentration of FX00 and FX03 in plasma. PK parameters including C_{max}, $AUC_{0\text{-}inf}$, CL/F, V_z/F,

$T_{1/2}$, and T_{max} will be calculated from plasma concentrations of FX00 and FX03. Additional PK parameters may be calculated if deemed appropriate.

4 SAMPLE SIZE

Approximately 24 subjects are planned to be randomized into the study, and 24 subjects are expected to complete the study. Subjects who do not comply with the protocol or who withdraw consent may be replaced. Additional subjects may replace early withdrawal subjects, unless the reason for discontinuation was a treatment emergent adverse event (TEAE).

Since the study is aimed at demonstrating safety of FX-322, the selected sample size was considered adequate for an initial assessment of safety and tolerability and was not based on formal statistical considerations such as power.

5 RANDOMIZATION

Subjects will be randomized to one of four treatment groups based on the randomization schedule prepared by the unblinded statistician.

Subjects will receive a single dose of either FX-322L, placeboL, FX-322H, or placeboH. Randomized subjects will be allocated 1:1 to one of 2 cohorts (12 in each cohort) and 2:1 allocation ratio to study drug (8 FX-322:4 placebo) within each cohort.

The otolaryngologist will be blinded to whether a patient is randomized to drug or placebo within a cohort, however, may not be blinded to the cohort (high dose or low dose) because low and high dose cohorts have different injection volumes.

6 PLANNED ANALYSES

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

6.1 Analysis Sets

Subjects excluded from the analysis sets and the reason for their exclusion will be listed in Appendix 16.2. For the purpose of analysis, subjects will be considered participating in the study if they are randomized.

6.1.1 Randomized Set

The Randomized Set includes all subjects who were randomly allocated to a treatment group.

6.1.2 Safety Analysis Set

The Safety Analysis Set (SAS) will include all subjects exposed to study drug and will be analyzed according to the actual treatment received regardless of the randomized treatment. The SAS will be used for safety analyses.

6.1.3 Per Protocol Analysis Set

The Per Protocol Analysis Set (PPAS) will consist of all subjects in the SAS who meet all of the inclusion and none of the exclusion criteria and have no major protocol deviations impacting the interpretation of the study results. Major protocol deviations potentially impacting the interpretation of the study results will be determined by the study team prior to breaking the blind. If different from the SAS, the PPAS may be used in additional analyses.

6.1.4 PK Analysis Set

All subjects in the SAS with measurable plasma concentrations will be included in the PK analysis set.

6.2 Derived Data

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

6.2.1 Race

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

6.2.2 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) that is collected before dosing.

6.2.3 Early Withdrawal Assessments

Data collected during Early Withdrawal assessments will be grouped and summarized separately from scheduled assessments. All Early Withdrawal data will be displayed as "Early Withdrawal" in the listings.

6.2.4 Duration/Study Day/Time

Study day will be calculated as the number of days from the single dose of study drug. The day of study drug dosing will be considered as Study Day 1.

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

6.2.5 Conventions for Missing and Partial Dates

It is not expected that there will be any missing dates, however in the rare case that an AE start date or time is missing and it is unclear whether the AE is treatment emergent or not then a conservative approach will be taken and it will be assumed that the AE occurred after first dosing.

All dates presented in the individual subject listings will be as recorded on the eCRF.

6.2.6 Inexact Values

In the case where a safety laboratory variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes. Original values, as reported by the analytical laboratory, will be presented in the listing.

6.2.7 Unscheduled Visits

Only scheduled post-baseline assessments will be tabulated. Post-baseline repeat/unscheduled assessments will be disregarded, although these post-baseline assessments will be listed in the relevant appendices to the CSR.

6.2.8 PK Parameters

Concentration-time data for FX00 and FX03 will be analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3 or higher, Certara, L.P.)[1].

During the pharmacokinetic analysis, concentrations below the limit of quantitation (BLQ) up to the time of the first quantifiable concentration will be treated as zero. Embedded (values between 2 quantifiable concentrations) and terminal BLQ concentrations will be treated as "missing".

Subjects receiving active treatment will be included in the PK analysis; subjects receiving placebo will be listed in the concentration-time listing by subject.

The following PK parameters will be calculated for FX00 and FX03:

C_{max}	Maximum concentration determined directly from individual concentration-time data; reported to 3 significant figures
T_{max}	Time to reach maximum concentration determined directly from individual concentration-time data; reported to 3 significant figures
AUC_{last}	Area under the concentration–time curve from time zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule; reported to 3 significant figures
AUC_{inf}	Area under the concentration–time curve extrapolated to infinity, calculated as: $AUC_{inf} = AUC_{last} + C_{last}/\lambda z$, where C_{last} is the last quantifiable concentration and λz is the terminal elimination rate constant; reported to 3 significant figures
AUC_{ex}	The percentage of AUC_{inf} based on extrapolation, calculated as: $\%AUC_{ex} = (AUC_{inf} - AUC_{last})/AUC_{inf}*100$; reported to 3 significant figures
$T_{½}$	The observed terminal elimination half-life calculated as: $T½ = \ln(2)/\lambda z$; reported to 3 significant figures
λz	The observed elimination rate constant; estimated by linear regression in the terminal phase of the log concentration-time profile; see additional criteria below; reported to 3 significant figures
CL/F	Apparent total body clearance after extravascular administration, calculated as: $CL/F = Dose/AUC_{inf}$; reported to 3 significant figures
Vz/F	Apparent volume of distribution following extravascular administration based on the terminal phase, calculated as: $Vz/F = (CL/F)/\lambda z$; reported to 3 significant figures

No value for λz and other λz-related parameters (AUC_{inf}, $T_{1/2}$, CL/F, etc.) will be reported if λz cannot be estimated.

6.2.9 Word Recognition (Quiet)

The percentage of words correctly identified out of a list of 50 words will be calculated for the Word Recognition (Quiet) test. If a subject has completed the assessment, it will be assumed that all 50 words were completed.

6.2.10 Identifying the Treated Ear

For assessments performed for each ear (left/right), the treated ear will be identified from the CRF and assessments will be presented by treated and untreated ear.

6.3 Conventions

All clinical data listings, summaries, figures and statistical analyses will be generated using SAS (Version 9.4 or higher)[2].

Summaries of the clinical data will be presented by treatment group and overall.

PK data listings, summaries, figures, and statistical analyses will be generated using Phoenix™ WinNonlin® (Version 6.3 or higher) or SAS (Version 9.4 or higher). PK concentration data will be summarized by analyte (FX00 and FX03), treatment (FX-322L or FX-322H), and overall at each nominal sample time.

Treatment group labels will be displayed as follows:

PlaceboL	PlaceboH	Pooled Placebo	FX-322L (0.05 mL)	FX-322H (0.20 mL)	Overall

Listings will be sorted in the following order: Treatment group [PlaceboL, PlaceboH, FX-322L (0.05 mL), FX-322H (0.20 mL)], subject, parameter, and visit unless otherwise stated. All data will be listed.

For clinical data, continuous variables will be summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum. A 95 % confidence interval (CI) will also be provided where change from baseline has been calculated.

The following summary statistics will be used to summarize the PK data (concentration-time data and PK parameters) by analyte (FX00 and FX03), treatment (FX-322L or FX-322H) and overall: the number of non-missing observations (n), mean, standard deviation (SD), median, minimum

(min), maximum (max), and coefficient of variation (CV%), calculated as (SD/Mean)*100. In addition, the geometric mean will be reported for C_{max} and AUCs. Where relevant, 95% confidence intervals for summary statistics will also be provided.

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

6.3.1 Decimal Places

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

For PK data, individual concentrations and parameter values will be reported to three significant figures and summarized by analyte (FX00 and FX03), treatment (FX-322L or FX-322H) and overall. For summary statistics, n will be reported as a whole number; mean, standard deviation, median, minimum, maximum, and geometric mean will be reported to the same precision as for individual data. CV% will be reported to two decimal places; p-values will be reported to four decimal places. Percent ratios of the geometric least squares means and associated 90% confidence intervals will be reported to two decimal places.

6.4 Subject Disposition

Subject disposition will be summarized as follows:

- The number of subjects in each analysis set will be summarized by treatment group and overall for the Randomized set.
- The number of early withdrawals and the reasons for withdrawal will be tabulated by treatment group for the Randomized set.

6.5 Protocol Deviations

A summary of major and minor protocol deviations will be tabulated by treatment group and overall. A detailed listing of protocol deviations will be provided within Appendix 16.2.

6.6 Baseline Comparability

The comparability of treatment groups with respect to subject demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed. The Safety Analysis Set will be used to summarize all baseline and demographic data.

6.7 Demographic data

Standard continuous or categorical variable summaries will be presented by treatment group for the following variables based on the Safety Analysis Set.

- Age at Informed Consent (years)
- Gender
- Ethnicity
- Race, where more than one race is selected the subject will be presented under the 'Multiple races' category in the summary but each selected race will be identified in the listing.
- Affected Ear (Left/Right/Both)
- Worst Ear (Left/Right)
- Treated Ear (Left/Right, Reason)
- Weight at Screening (kg)
- Height at Screening (cm)
- BMI at Screening (kg/m^2)
- Fertility Status

6.8 Medical History

Previous and ongoing conditions at baseline will be tabulated by treatment group and overall for the Safety Analysis Set. Conditions will be coded using the Medical Dictionary of Regulated Activities (MedDRA version 20.0 March 2017) primary system organ class and preferred term. Any medical condition will be classed as resolved if a stop date is recorded, otherwise, the condition will be classed as ongoing. Prior conditions are defined as all conditions starting and stopping before the date of first dose of study drug. Ongoing conditions are defined as conditions present on or after the date of first dose of study drug.

6.9 Prior and Concomitant Medications

The number and percentage of subjects using concomitant medications will be tabulated using drug class and preferred drug name by treatment group and overall for the Safety Analysis Set.

All prior and concomitant medications will be listed. Prior medications are defined as all medications starting and stopping before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug.

All medications will be coded using the World Health Organization Drug Dictionary (WHO Drug Dictionary version March 2017) ATC Level 2 class and preferred term.

6.10 Exposure to Study Drug

All dosing information will be listed.

6.11 Pharmacokinetic Analyses

Blood samples for plasma pharmacokinetic (PK) analysis will be obtained at pre-dose, 0.5 hour (+/-10 min), 1 hour (+/- 15 min), 2 hour (+/- 15 min), 4 hour (+/- 15 min), 8 hour (+/- 15 min), and 24 hours (+4 hours) post injection.

Concentration-time data will be tabulated by analyte (FX00 and FX03), treatment and nominal time using descriptive statistics. For presentation of the individual data and summary statistics, concentrations below the limit of quantitation (BLQ) will be set to zero.

Mean and individual plasma concentration-time data will be presented graphically on both linear and semi-log scales. Spaghetti plots (all subjects in one plot) will be presented by analyte (FX00 and FX03), treatment, and overall on both linear and semi-log scales. Mean data will be plotted using nominal sample times, and individual data will be plotted using actual times.

PK parameters for FX00 and FX03 will be calculated as described in Section 6.2.8.

6.12 Biomarker Analysis

All blood sampling information for biomarker analysis will be listed.

6.13 Safety Analyses

The safety analyses will be presented by the treatment received for the Safety Analysis Set.

6.13.1 Adverse Events

A treatment emergent adverse event (TEAE) is defined as:

- Any AE that has an onset on or after the single dose of study drug through the final follow-up visit (Day 90).
- Any pre-existing AE that has worsened in severity on or after the single dose of study drug through the final follow-up visit (Day 90).

Relatedness of an AE to treatment can be recorded as Unrelated, Unlikely, Possible or Probable. A treatment-related AE is defined as any AE classified as possibly or probably related to the study drug. If an AE has missing relationship it is assumed to be related to the study drug for analysis purposes.

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

The following tables will be presented for AEs:

- Overall incidence and the number of TEAEs, TEAEs of the Ear, Severe TEAEs, SAEs, TEAEs leading to withdrawal and TEAEs leading to Death
- TEAE by system organ class and preferred term, incidence
- Serious TEAE by system organ class and preferred term, incidence
- TEAE by system organ class, preferred term and maximum severity, incidence
- TEAE by system organ class, preferred term and relationship, incidence
- TEAE of the Ear by system organ class, preferred term and treatment status of the ear, incidence
- TEAEs leading to Early Withdrawal by system organ class and preferred term, incidence
- Listing of Serious TEAEs (presented in the Table section of the appendices)
- Listing of Deaths (presented in the Table section of the appendices)

System organ class will be presented in descending order of overall frequency and then alphabetically. Preferred terms will be displayed in descending order of overall frequency and then alphabetically.

Subjects reporting more than one AE per system organ class and preferred term will only be counted once. For analyses concerning severity of the event or relatedness to study drug, the most severe event or the most related event will be used.

All AEs will be listed.

6.13.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline (continuous data) will be presented by treatment group and visit for each hematology, serum chemistry, coagulation and urinalysis parameter. Each measurement (continuous data) will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented. Categorical data will be presented by treatment group and follow-up visit.

A listing of any clinically significant laboratory measurements recorded throughout the study will be presented.

All laboratory data, including serology, urine drug and alcohol screening and pregnancy data will be listed.

6.13.3 Vital Signs

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

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Respiration rate (breath/min)
- Body temperature (degrees Celsius)
- Body weight (kg)

All vital sign data will be listed.

6.13.4 Electrocardiogram Data

Descriptive statistics for observed values in the following ECG variables will be tabulated by treatment group and overall at the baseline visit and each follow-up visit:

- Heart rate (bpm)
- PR interval (ms)
- RR interval (ms)
- QRS complex (ms)
- QT interval (ms)

- QTc interval (ms)
- QTc interval (ms) [Bazett's formula - QTcB]
- QTc interval (ms) [Fridericia's formula - QTcF]

Overall interpretation (Normal, Abnormal NCS, and Abnormal CS) will be tabulated by treatment group and overall for the Baseline visit and each follow-up visit.

All ECG data, including details of any abnormalities, will be listed.

6.13.5 Physical Examination

Summaries for the observed status of each of the body systems (Normal, Abnormal NCS, and Abnormal CS) will be tabulated by treatment group and overall for the Baseline visit and for each follow-up visit. All data, including details of clinically significant findings will be listed.

6.13.6 Tympanometry and Otoscopy Assessments

Summaries for each element of the tympanometry and otoscopy assessments will be tabulated by treatment group and overall at each visit for the treated and untreated ear. Changes from baseline and shifts in status from baseline to each follow-up visit will also be tabulated. All data, including details of any abnormalities, will be listed.

6.13.7 Comprehensive Audiogram Assessment

Summaries of data obtained for each frequency will be tabulated by treatment group and overall at each visit for the treated and untreated ear. Changes from baseline will also be tabulated. All data will be listed including correction factors and any frequencies attempted but not obtained.

6.13.8 Word Recognition and Words-In-Noise Assessments

The percentage of words correctly identified out of a list of 50 words will be summarized for the Word Recognition (Quiet) test. The number of words correctly identified will be summarized for the Words-in-Noise Test (WIN). Summaries will be tabulated by treatment group and overall at each visit. Changes from baseline will also be tabulated.

Categorical analysis of the change from baseline will also be performed for the Word Recognition (Quiet) test. Percentage scores obtained at each follow-up visit will be classified as Improved, No Change or Worsening according to the table of 95% Critical Differences in Appendix 1. Values within the range shown are not significantly different from the value shown in the percentage score

columns ($p > 0.05$). Values falling below the stated range will be considered Worsening and values exceeding the stated range will be considered Improved. All data will be listed.

6.13.9 Interval Noise History

All interval noise history data will be listed.

7 BLIND SAFETY DATA REVIEW

A blind Safety Data Review will be performed when all subjects have completed the Day 15 follow-up assessment. Subject disposition, demographic data, medical history, treatment-emergent adverse events, laboratory data, tympanometry, otoscopy and audiometry data will be summarized for all subjects. Required outputs are marked with an asterisk in the list of Tables, Figures and Listings. Outputs will be produced using the same shells as for the End of Study with one Overall column to ensure the blind is maintained.

8 CHANGES TO PLANNED PROTOCOL ANALYSIS

A blind Safety Data Review will be performed that was not previously detailed in the protocol but was requested by the Sponsor. The rationale for the analysis is that completion of the Day 15 visit will be the first opportunity to review safety endpoints for all subjects.

9 REFERENCES

1. Phoenix™ WinNonlin® (Version 6.3, Certara L.P.)
2. SAS Institute Inc., Cary, NC, 27513, USA
3. Thornton AR, Raffin MJ (1978) *J Speech Hear Res.*, Sep; 21(3): 507-18.

10 LIST OF TABLES, FIGURES AND LISTINGS

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

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

Table Number	Table Title	Validation Method	Shell Number (if repeat)
Items in bold are not table titles but references to the section headings within eCTD.			
14.1	**Demographics Data**		
14.1.1	**Disposition**		
14.1.1.1*	Subject Disposition, Early Withdrawals – Randomized Set	IP	
14.1.2	**Demographics**		
14.1.2.1*	Demographics, Safety Analysis Set	IP	
14.1.3	**Baseline Characteristics**		
14.1.3.1*	Medical History Prior to Baseline – Safety Analysis Set	IP	
14.1.3.2*	Medical History Ongoing at Baseline – Safety Analysis Set	IP	
14.1.3.3	Physical Examination at Screening – Safety Analysis Set	IP	
14.1.3.4	ECG Data at Baseline – Safety Analysis Set	IP	
14.2	**Safety Data**		
	Not Applicable		
14.3	**Safety Data**		
14.3.1	**Displays Of Adverse Events**		
14.3.1.1*	Summary Of Treatment-Emergent Adverse Events (TEAEs) – Safety Analysis Set	IP	
14.3.1.2*	TEAEs By Primary System Organ Class And Preferred Term – Safety Analysis Set	IP	
14.3.1.3*	Serious TEAEs By Primary System Organ Class And Preferred Term – Safety Analysis Set	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.1.4*	TEAEs By Primary System Organ Class Preferred Term And Severity – Safety Analysis Set	IP	
14.3.1.5*	TEAEs By Primary System Organ Class Preferred Term And Relationship – Safety Analysis Set	IP	
14.3.1.6*	TEAEs Of The Ear By Primary System Organ Class Preferred Term And Treatment Status – Safety Analysis Set	IP	
14.3.1.7*	TEAEs Leading To Early Withdrawal By Primary System Organ Class And Preferred Term – Safety Analysis Set	IP	
14.3.2	**Listings Of Deaths, Other Serious And Significant Adverse Events**		
14.3.2.1*	Serious TEAEs, Listing– Safety Analysis Set	IP	
14.3.2.2*	Deaths, Listing – Safety Analysis Set	IP	
14.3.3	**Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events** (Placeholder should be maintained and tables/figures should not be numbered to appear in this section)		
14.3.4	**Abnormal Laboratory Values**		
14.3.4.1*	Listing of Clinically Significant Laboratory Values – Safety Analysis Set	IP	
14.3.5	**Extent Of Exposure, Dosage Information, And Compliance**		
	Not Applicable		
14.3.6	**Vital Signs And Physical Examination**		
14.3.6.1	Vital Signs, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7	**Other Safety**		
14.3.7.1*	Hematology Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.2*	Hematology Data, Normal Range Shifts – Safety Analysis Set	IP	
14.3.7.3*	Serum Chemistry Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.4*	Serum Chemistry Data, Normal Range Shifts – Safety Analysis Set	IP	

Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.3.7.5*	Coagulation Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.6*	Coagulation Data, Normal Range Shifts – Safety Analysis Set	IP	
14.3.7.7*	Urinalysis Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.8*	Urinalysis Data, Normal Range Shifts – Safety Analysis Set	IP	
14.3.7.9	ECG Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.10	ECG Data, Overall Interpretation – Safety Analysis Set	IP	
14.3.7.11*	Tympanometry Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.12*	Otoscopy Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.13*	Comprehensive Audiometry Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.14	Word Recognition (Quiet) Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.7.15	Words-In-Noise Data, Descriptive Statistics – Safety Analysis Set	IP	
14.3.8	**Concomitant Medication**		
14.3.8.1	Concomitant Medication Data – Safety Analysis Set	IP	
14.4	**PK Tables**		
14.4.1	FX00 and FX03 Concentration-Time Data, Descriptive Statistics – PK Analysis Set		
14.4.2	FX00 and FX03 Pharmacokinetic Parameters, Listing and Descriptive Statistics – PK Analysis Set		

Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4.1	Mean FX00 and FX03 Concentration Time Data on Linear and Semi-Logarithmic Scales – PK Analysis Set		
14.4.2	FX00 and FX03 Concentration-Time Data, All Subject Profiles on Linear and Semi-Logarithmic Scales – PK Analysis Set		
14.4.3	Concentration-Time Profiles for FX00 and FX03 with Linear Regression for Estimating the Terminal Elimination Rate – PK Analysis Set		

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	**Subject Data Listings**		
16.2.1	**Discontinued Subjects**		
16.2.1.1*	Subject Disposition, Early Withdrawals – Randomized Set	IP	
16.2.2	**Protocol Deviations**		
16.2.2.1	Protocol Deviations – Safety Analysis Set	IP	
16.2.3	**Subjects Excluded From The Efficacy Analyses**		
16.2.3.1	Analysis Sets – Randomized Set	IP	
16.2.4	**Demographic Data**		
16.2.4.1*	Demographic Data – Safety Analysis Set	IP	
16.2.4.2*	Previous and Ongoing Medical History – Safety Analysis Set	IP	
16.2.5	**Compliance And/Or Drug Concentration Data**		
16.2.5.1	PK Sampling Data – Safety Analysis Set	IP	
16.2.5.2	Biomarker Sampling Data – Safety Analysis Set	IP	
16.2.5.3	Prior and Concomitant Medication – Safety Analysis Set	IP	
16.2.5.4	Dosing Information – Safety Analysis Set	IP	
16.2.6	**Individual Efficacy Response Data**		
16.2.6.1	FX00 and FX03 Concentration Listing by Subject – Safety Analysis Set		
16.2.6.2	Plasma Terminal Elimination Rate of FX00 and FX03 for Individual Subjects – PK Analysis Set		
16.2.6.3	PK Output Text		
16.2.7	**Adverse Event Listings**		
16.2.7.1*	Adverse Event Data – Safety Analysis Set	IP	
16.2.8	**Individual Laboratory Measurements And Other Safety**		
16.2.8.1*	Hematology Data – Safety Analysis Set	IP	
16.2.8.2*	Serum Chemistry Data – Safety Analysis Set	IP	
16.2.8.3*	Coagulation Data – Safety Analysis Set	IP	
16.2.8.4*	Urinalysis Data – Safety Analysis Set	IP	
16.2.8.5	Other Clinical Laboratory Data – Safety Analysis Set	IP	
16.2.8.6	Vital Signs Data – Safety Analysis Set	IP	
16.2.8.7	Physical Examination Data – Safety Analysis Set	IP	

Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.8.8	ECG Data – Safety Analysis Set	IP	
16.2.8.9*	Tympanometry Data – Safety Analysis Set	IP	
16.2.8.10*	Otoscopy Data – Safety Analysis Set	IP	
16.2.8.11*	Comprehensive Audiometry Data – Safety Analysis Set	IP	
16.2.8.12	Word Recognition (Quiet) Data – Safety Analysis Set	IP	
16.2.8.13	Words-In-Noise Data – Safety Analysis Set	IP	
16.2.8.14	Interval Noise History – Safety Analysis Set	IP	

APPENDIX 1

Lower and Upper Limits of the 95% Critical Differences for Percentage scores for Word Recognition (Quiet) Test[3].

Values within the range shown are not significantly different from the value shown in the percentage score columns ($p > 0.05$).

% Score	n = 50
0	0 - 4
2	0 - 10
4	0 - 14
6	2 - 18
8	2 - 22
10	2 - 24
12	4 - 26
14	4 - 30
16	6 - 32
18	6 - 34
20	8 - 36
22	8 - 40
24	10 - 42
26	12 - 44
28	14 - 46
30	14 - 48
32	16 - 50
34	18 - 52
36	20 - 54
38	22 - 56
40	22 - 58
42	24 - 60
44	26 - 62
46	28 - 64
48	30 - 66
50	32 - 68
52	34 - 70

54	36 - 72
56	38 - 74
58	40 - 76
60	42 - 78
62	44 - 78
64	46 - 80
66	48 - 82
68	50 - 84
70	52 - 86
72	54 - 86
74	56 - 88
76	58 - 90
78	60 - 92
80	64 - 92
82	66 - 94
84	68 - 94
86	70 - 96
88	74 - 96
90	76 - 98
92	78 - 98
94	82 - 98
96	86 - 100
98	90 - 100
100	96 - 100