CLINICAL STUDY PROTOCOL

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

EudraCT Number: N/A

Investigational Product: FX-322

Phase: Phase 1/2

Sponsor: Frequency Therapeutics
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Protocol Date: 02 Aug 2018

Protocol Version: Version 3.0

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1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: 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

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

[redacted]

[redacted]

Signature

[redacted]

Date

2 SYNOPSIS

Protocol Number:

FX-322-201

Title:

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

Investigational Product:

FX-322

Study Centers:

2-5 centers in the US

Phase:

Phase 1/2

Objectives:

Primary objectives:

- 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

Study Design:

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 6 months of 10 dB or more in any frequency). The 2 dose levels proposed in this study, FX-322L and FX-322H will be dosed concurrently.

The study will have 3 phases: Screening, Treatment with Observation, and Follow-up.

Screening: Can occur up to 30 days prior to study drug administration (Day 1). All subjects will be screened to determine study eligibility.

Double Blind Treatment with Observation: Approximately 24 subjects are planned to be randomized to one of four treatment groups to 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.

The study treatment will be administered on Day 1 by an intratympanic injection.

The investigational drug, FX-322, is a fixed ratio dose combination of two small molecules: a glycogen synthase kinase (GSK) inhibitor, FX03, and Valproate Sodium (FX00) (a histone deacetylase inhibitor; HDAC inhibitor). There will be a matched placebo, identical in consistency and color to FX-322.

Once a subject has been identified, as meeting all inclusion/exclusion criteria, the ear with the worse hearing will be selected, unless a rationale exists to treat the other ear. The Investigator will need to discuss that rationale with the Sponsor prior to randomization.

Each subject will be placed in the supine position. EMLA® topical anesthetic cream will be administered to the tympanic membrane using the provided applicator kit. The cream will cover the eardrum and remain in place for 2-3 minutes then suctioned clear. 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 10-15 minutes. The injections will be performed at an appropriate location designated by a Board Certified Otolaryngologist trained and experienced in performing intratympanic injections.

The 24 subjects will be required to stay in the Phase 1 Unit overnight for observation for up to 28 hours post injection.

Blood samples for plasma pharmacokinetic (PK) 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.

Safety monitoring will include recording of adverse events (AEs) and 12-lead electrocardiogram (ECG) findings at baseline, 1 hour (+/-30 min), and 24 hours post injection.

Safety labs and urine testing will be collected per the Schedule of Events.

In addition, a blood sample will be taken for exploratory biomarker analysis prior to, 24 hours post, 15 days post and 3 months post injection.

Follow up: Subject will be required to return for safety, otologic, and audiologic assessments 2 weeks post injection. Subjects will return at 1, 2, and 3 months for otoscopic and audiologic assessments.

Number of Subjects:

Approximately 24 evaluable subjects

Study Duration:

Screening phase: up to 30 days before study drug administration.

Treatment with observation phase: 1 day (up to 28 hours)

Follow-up phase: 3 months

Study Population:

Male and female adults, 18 to 65 years, inclusive, otherwise healthy with stable sensorineural hearing loss

Primary Endpoint(s):

- 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

Pharmacokinetics:

Blood samples for determination of plasma concentrations will be drawn pre-dose and 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. Calculated PK parameters include C_{max}, AUC0-inf, CL, V_{ss}, T1/2, and T_{max}.

Safety:

Safety assessments including adverse events, laboratory parameters, vital signs, physical examination, ECG, audiometry, and otoscopy.

Statistical Analysis:

Sample Size: 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. As such, the statistical analyses will consist of descriptive statistics including the mean, standard deviation (SD), median, minimum and maximum statistics for continuous endpoints and numbers and percent for categorical endpoints. Where relevant, 95% confidence intervals will also be provided.

Statistical Methods: Subjects will be randomized to one of four treatment groups: FX-322L, PlaceboL, FX-322H, or PlaceboH using a 1:1 allocation ratio for dose cohort (12 per cohort) and within each cohort a 2:1 allocation ratio for study drug (8 FX-322: 4 placebo). Since the volume in the syringe may be potentially unblinding to the otolaryngologist, for this study, cohort assignment may not be blinded to the otolaryngologist (all subjects and study staff will remain blinded), and randomization to FX-322 or placebo will remain double-blind to all study staff (including the otolaryngologist) and subjects. Patient disposition, demographic and medical history will be tabulated. Summary tabulations for treatment-emergent adverse events will be presented by preferred term and body system using the Medical Dictionary for Regulatory Activities (MedDRA®). Tabulations will be provided by seriousness, severity, and relationship to study drug. Laboratory data will be presented as summary statistics at each timepoint measured as well as changes from baseline and/or shift tables. Otologic and audiologic endpoints will be summarized in a similar manner. Pharmacokinetics will summarize the PK parameters for relevant endpoints and present individual as well as summary FX-322 concentration-time profiles. All subjects exposed to study drug will be included in the Safety Analysis Set and included in the safety analyses according to the treatment received regardless of the randomized assignment. While statistical tests may be conducted, given the lack of formal consideration for statistical power, these will be viewed as exploratory analyses rather than confirmatory. Details of the planned statistical analyses and methods will be provided in the Statistical Analysis Plan (SAP).

PROTOCOL Version 3.0 Amendments

Item No.	Change	Section and Page Number(s)
1	Updated date and version of protocol.	Title Page, pg.1 Footer, every page
2	Updated Day 15 Visit window to +/- 3 days.	Table 1. pg. XX Section 8.1.4. Day 15 Visit, pg.
3	Updated Vitals to sitting and removed supine	Section 8.1.1. Screening Visit, pg. 12
4	Added coagulation to the testing to be performed.	Section 8.1.2. Baseline/Treatment Visit, pg. 21
5	Updated drug testing to naming of the tests performed at site.	Section 8.1.1. Screening Visit, pg. 17 Section 9.1.2. Clinical Laboratory Evaluation, pg. 21
6	Updated the Day 50 Visit to Day 60 to correct error.	Section 9.2.3.Word Recognition. pg. 21
7	Added “or back up designee” to ensure coverage if Medical Monitor is not available..	Section 8.1.1.Screening Visit. pg. 21

PROTOCOL 2.0

Item No.	Change	Section and Page Number(s)
1	Updated date and version of protocol.	Title Page, pg.1 Footer, every page
2	Updated Sponsor Signatory.	Name and contact information, pg. 2
3	Clarified type of topical anesthetic to EMLA.	Synopsis, pg. 4 Section 7.1 Overall Study Design and Plan: Description, pg. 12 Section 7.4.1 Investigational Products Administered, pg. 17 Section 7.6.5 Selection and Timing of Dose for Each Subject, pg. 21
4	Clarified location of the intratympanic injection.	Synopsis, pg. 4 Section 7.1 Overall Study Design and Plan: Description, pg. 12 Section 7.4.1 Investigational Products Administered, pg. 17 Section 7.6.5 Selection and Timing of Dose for Each Subject, pg. 21
5	Updated Table of Contents.	Table of Contents, pg. 7-9
6	Updated list of abbreviations.	Abbreviations, pg. 11
7	Updated Table 1: Schedule of Assessments.	Table 1: Schedule of Assessments, pg. 14
8	Added additional exclusion criteria	Section 7.3.3 Exclusion Criteria pg.15
9	Removed “use of insulin (by any route)” .	Section 7.6.7 Prohibited Medication/Therapy, pg.21
10	Added additional Words-In-Noise (WIN) testing to applicable visits.	Section 8.1.1 Screening Visit, pg. 22 Section 8.1.4 Follow-up Visit 4, pg. 23 Section 8.1.5 Follow-up Visits 5, 6, and 7, pg. 23
11	Added description of Words-In-Noise (WIN) testing.	Section 9.2.4, pg. 27
12	Added reference for WIN testing	Section 15 References, pg. 38

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ASHA	American Speech-Language-Hearing Association
BMI	Body mass index
BPPV	Benign Paroxysmal Positional Vertigo
CNIHL	Chronic noise induced hearing loss
CL	Total clearance
C_{max}	Maximal plasma concentration
CRO	Contract Research Organization
dB	decibel
DMSO	Dimethyl sulfoxide
DPOAE	Distortion product otoacoustic emissions
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
GCP	Good Clinical Practice
GSK	Glycogen Synthase Kinase
HDAC	Histone deacetylase
HCG	Human chorionic gonadotrophin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intrauterine device
LGR5+	Leucine-rich repeat-containing G-protein coupled receptor 5
MedDRA ®	Medical Dictionary for Regulatory Activities
PE	Physical exam
PI	Principal Investigator
PK	Pharmacokinetics
QTcF	QT interval data corrected using Fridericia's formula
SAE	Serious Adverse Event
SD	Standard deviation
SNHL	Sensorineural hearing loss
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximal concentration
TM	Tympanic membrane
Vss	Apparent volume of distribution at steady state
WHO	World Health Organization
WIN	Words-In-Noise Testing

5 INTRODUCTION

Worldwide, an estimated 1.1 billion people are at risk for hearing loss due to exposure to damaging levels of sound (WHO, 2015). Excessive sound levels or loud sounds for extended periods time hyperstimulate cochlear hair cells, which can lead to increased production of reactive oxygen species and oxidative cell death. Structural damage to hair cells results in sensorineural hearing loss (SNHL), which can be characterized by an attenuation and distortion of response to incoming auditory stimuli. Presently, no curative treatments exist, but rather assistive devices such as hearing aids and cochlear implants are used to address the symptoms of SNHL. These options, however, do not address the cause of SNHL and are not sufficient for normal quality of life in individuals with SNHL.

Sensorineural hearing loss (SNHL) accounts for about 90% of all cases of hearing loss (Li et al, 2017). Leading causes include noise exposure, ototoxic medications, advanced age, inherited, and autoimmune disorders. SNHL is usually irreversible and managed with hearing aids or cochlear implants. Noise is a major occupational and environmental hazard, causing hearing loss, sleep disturbance, fatigue, and hypertension (Hong et al, 2013). SNHL has long been recognized as the primary and direct health effect of excessive noise exposure (Basner et al, 2015). In the United States, an estimated 48 million people or 20.3% of the population 12 years or older has hearing loss in one or both ears (Lin et al, 2011). The World Health Organization reported that 16% of the disabling hearing loss in adults is attributable to occupational noise exposure (Nelson et al, 2005). Hearing loss is associated with increased dementia, depression, and other mental health disorders, especially in the elderly (Choi et al, 2016; McGilton et al, 2016; Deal et al, 2016).

FX-322 is a fixed ratio dose combination of two small molecules: a glycogen synthase kinase (GSK) inhibitor, FX03, and Valproate Sodium (an HDAC inhibitor approved in multiple countries including the US for human use as Depacon®).

The active ingredients in FX-322 target two cellular mechanisms, histone deacetylase (HDAC) and GSK inhibition, which act synergistically to induce a regenerative response in cochlear tissue and thus may restore hearing function in subjects with hearing loss including CNIHL. Leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5+) progenitor cells have the capability of asymmetric division to create a copy of themselves and a daughter cell that can become a hair cell.

In preclinical experiments, a fixed ratio dose combination of FX03 and Valproate Sodium demonstrates:

- Expansion of the Lgr5+ progenitor cells and formation of new hair cells in cell culture studies in newborn and adult mice. Substantial Lgr5+ expansion occurs with the combination of agents but not with the individual agents alone.
- Expansion of progenitor cells in adult primate and adult human inner ear tissue.
- Formation of new hair cells in explanted mouse cochlea cultures.
- Significant improvement in hearing and increase in hair cell count in an adult mouse model of noise-induced hearing loss maintained for at least 3 months after a single treatment.

Based on these findings, FX-322 is formulated as a fixed ratio dose combination, [redacted]

[redacted]r. FX-322 will be administered by an intra-tympanic injection into the middle ear onto the round window membrane area, for the active ingredients to be locally absorbed into the cochlea. Systemic exposure from local deposition of the drug in the gel is expected to be negligible. There has been one clinical study performed with FX-322, study FX-322-103. Nine patients undergoing cochlear implantation surgery received a single unilateral intra-tympanic injection of FX-322 (6 patients) or placebo (3 patients) to study the uptake in the cochlea. The results demonstrated acceptable local and systemic acute safety and tolerability and very limited systemic exposure after the local intra-tympanic injection which was unmeasurable within 24 hours post injection. In addition, the cochlear pharmacokinetic (PK) data demonstrated the drug was present at 4 h post-IT injection in one patient but unmeasurable after 24 hours in the perilymph in two subjects.

6 STUDY OBJECTIVES

6.1 Primary Objective(s)

- 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

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan: Description

This is a Phase 1/2 randomized, double-blind, placebo-controlled, single dose study to evaluate the safety at two dose levels of FX-322L and FX-322H compared to placebo in adults with stable sensorineural hearing loss (no changes over 6 months of 10 dB or more in any frequency). The trial will have three phases: Screening, Treatment with Observation, and Follow up.

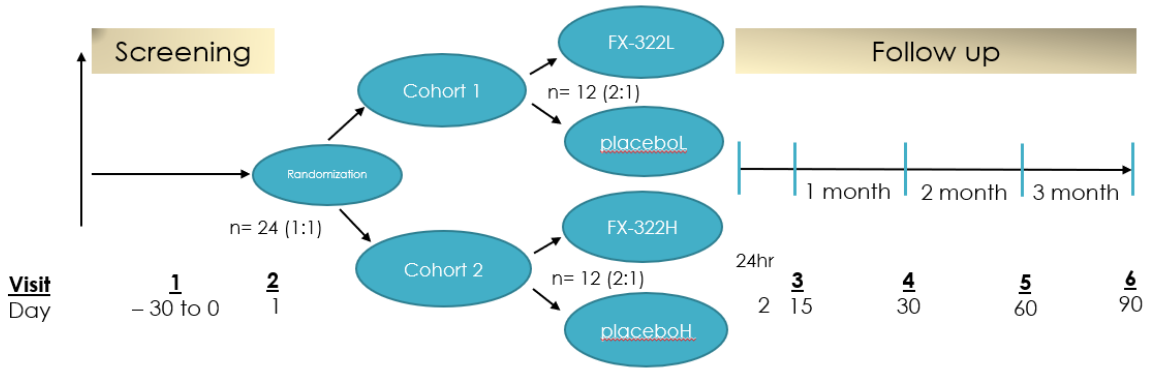
Screening: Can occur up to 30 days prior to study drug administration (Day 1). All subjects will be screened to determine study eligibility.

Double Blind Treatment: Treatment with Observation: Approximately 24 subjects are planned to be randomized using a 1:1 allocation ratio to cohort (12 in each cohort) and a 2:1 allocation ratio to study drug (8 FX-322:4 placebo) within each cohort. Subjects will be randomized to one of four treatment groups to receive a single dose of either FX-322L, placeboL, FX-322H, or placeboH.
Each subject will be placed in the supine position. EMLA® topical anesthetic cream will be administered to the tympanic membrane using the provided applicator kit. The cream will cover the eardrum and remain in place for 2-3 minutes then suctioned clear. Under a microscope, a 25-gauge needle will be used to inject of 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 10-15 minutes. The injections will be performed at an appropriate location designated by a Board Certified Otolaryngologist trained and experienced in performing intratympanic injections. The 24 subjects will be required to stay in the Phase 1 Unit overnight for observation for up to 28 hours post injection.
Blood samples for plasma pharmacokinetic (PK) will be obtained pre-dose and at 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.
Safety monitoring will include recording of adverse events (AEs) and 12-lead electrocardiogram (ECG) findings at baseline (pre-dose), 1 hour (+/- 30 mins), and 24 hours post injection. Safety labs and urine testing will be collected per the Schedule of Events.
In addition, a blood sample will be taken for exploratory biomarker analysis prior to and 24 hours post, 15 days post, and 3 months post injection.

Follow up: Subject will be required to return for safety, otologic, and audiologic assessments 2 weeks post injection. Subjects will return at 1, 2, and 3 months for otoscopic and audiologic assessments.

7.1.1 Study Design



7.1.2 Schedule of Assessments

The schedule of planned study assessments is shown in Table 1.

Table 1: Schedule of Assessments

Visit	**Screening**	**Treatment**	**Observation**	**Follow-up**	
Assessment/Day	**-30 to 0**	**1**	**2**	**15 (+/-3 days)**	**30,60,90** [h]
Informed Consent	X				
Inclusion/ Exclusion Criteria	X	X			
Demographics	X				
Medical History	X	X			
Interval noise history				X [g]	X [g]
Concomitant Medication	X	X[a]	X	X	X
Physical Examination including weight and height	X				
Vital Signs (body temperature, pulse rate, bp)	X	X[a]	X	X	X
ECG (12–lead)	X	X[c]	X[c]		
Tympanometry	X			X	X
Comprehensive audiogram	X	X[b]		X	X
Word Recognition, quiet	X			X	X
Words-In-Noise Testing (WIN)	X			X	X
Otoscopy	X	X[a]		X	X
Safety blood samples	X	X[a]	X	X	
Hepatitis B and C testing	X				
Urinalysis	X	X[a]	X	X	
Urine Pregnancy Test (women of child bearing potential only)	X	X[a]		X	X
Drug Screen	X[d]				
PK: Plasma FX-322		XXXXXX[f]	X		
Blood sample for biomarker analysis		X[a]	X	X	X[i]
Randomization		X[j]			
Study Medication (FX-322 or Placebo injection)		X			
Adverse Events		X[e]	X	X	X

Subjects will be given the option of staying overnight the day before dosing (Day 1)

a- Assessment performed prior to injection.
b- Assessment performed up to 24 hr. prior to injection with a standard audiogram
c- 12-lead ECG to be performed in a supine position prior to injection, 1 hour post injection (+/-30 mins), and 24 hours
d- Should there be a positive result from the battery of drug screen tests, and the Investigator feels the subject should not be excluded, the Sponsor will be contacted to determine final eligibility.
e- Assessments performed after injection
f -Time points: prior to injection and 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.
g- Interval noise history will be collected by querying the subject about noise exposure since receiving study treatment
h- Visit windows: +/- 5 day for all visits
i- Perform only at the Follow Up Day 90 Visit
j-Randomization will occur on Day 1 prior to study drug administration.

7.2 Discussion of Study Design

This is a Phase 1/2 randomized, double-blind, placebo-controlled, single dose study to evaluate the safety at two dose levels of FX-322 (FX-322L and FX-322H) compared to placebo in adults with stable sensorineural hearing loss (no changes of 10 dB or more in any frequency at least 6 months prior to screening).

7.3 Selection of Study Population

7.3.1 Number of Planned Subjects

Approximately 24 subjects are planned to enter the study, and 24 subjects are expected to complete the study. Additional subjects will be enrolled to account for early termination/withdrawal subjects, unless the reason for discontinuation was a treatment emergent adverse event.

7.3.2 Inclusion Criteria

To be eligible for study entry subjects must satisfy all of the following criteria:

1. Subject has read and voluntarily signed the Informed Consent Form (ICF) after all questions have been answered and prior to any study-mandated procedure.
2. Adult aged 18-65 years.
3. Established diagnosis of stable sensorineural hearing loss (no changes of 10 dB or more in any frequency) by standard audiometric measures for >6 months.
4. Documented medical history consistent with hearing loss being caused by noise exposure or sudden sensorineural hearing loss (documented audiogram at least 6 months prior to screening required).
5. Ability to communicate well with the Investigator and is willing to comply with and complete all the study procedures.
6. Female subjects must be of non-childbearing potential or will need to utilize two methods of highly effective contraception during the study participation (e.g. hormonal contraception or an intrauterine device and condoms) or remain abstinent. Male subjects should use condoms with spermicide during the course of the study or remain abstinent. Subjects should not donate sperm or ova during the study period.

7.3.3 Exclusion Criteria

Subjects will be excluded from the study if one or more of the following criterion are applicable:

1. Subjects currently on any medication consisting of valproic acid, valproate sodium, or divalproex sodium (e.g. Depacon®, Depakote®, Depakene, Epival®, Valpro, and Epilim).
2. Perforation of tympanic membrane or other tympanic membrane disorders that would interfere with the delivery and safety assessment of an intratympanic medication or reasonably be suspected to affect tympanic membrane healing after injection in either ear. This includes a current tympanostomy tubes.
3. Any conductive hearing loss of 10 dB or more at two or more frequencies in either ear.

4. A pure tone average of 70 dB or greater at 500Hz, 1000Hz, 2000Hz, and 4000Hz in the ear to be injected.
5. Active chronic middle ear disease or a history of major middle ear surgery, as an adult, in the ear to be injected.
6. Subject has had an intratympanic injection in either ear within 6 months of the screening visit.
7. History of clinically significant vestibular symptoms at the discretion of the investigator. For example, BPPV may be considered acceptable whereas Ménière's would not.
8. History of clinically significant systemic autoimmune disease (e.g. rheumatoid arthritis, Sjogren's syndrome, multiple sclerosis, psoriasis).
9. History of head or neck radiation treatment or exposure.
10. Exposure to another investigational drug within 28 days prior to injection of study drug.
11. Evidence of any active or chronic disease, or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature), 12-lead ECG, and clinical laboratory parameters (hematology, blood chemistry, and urinalysis)). Deviations of laboratory values from the normal range may be accepted, if judged by the Investigator to have no clinical relevance. In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects in the opinion of the Investigator.
12. History of substance abuse within 2 years of the Screening Visit.
13. Positive test for drugs of abuse at screening. In cases when the Investigator feels the subject should not be excluded for a positive drug test, the Sponsor will be consulted and determine final eligibility.
14. Positive urine pregnancy test or breast-feeding.
15. Any known factor, condition or disease that, in the view of the investigator, might interfere with treatment compliance, study conduct or interpretation of the results such as psychiatric disease or suicidal tendencies.

7.3.4 Withdrawal of Subjects From Assessments

Subjects may stop the study for any of the following reasons:

- Subject request
- Use of non-permitted concurrent therapy
- Non-compliance with the study schedule
- Lost to follow-up
- Occurrence of adverse events (AEs) not compatible with the continuation of subject participation in the study, in the investigator's opinion, or unacceptable to the subject to continue
- Investigator request
- Intercurrent illness
- Sponsor request
- Pregnancy

Subjects who do not comply with the protocol or who withdraw consent may be replaced. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the case report form (CRF). Any subjects that withdraw due to a treatment emergent adverse event (TEAE) will not be replaced.

Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

Pregnancy

Subjects will be instructed that known or suspected pregnancy occurring during the study, in subjects or female partners of male subjects, should be confirmed and reported to the investigator. All subjects will be followed until the end of the study, completing study assessments as appropriate during pregnancy. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the sponsor after delivery.

Full details will be recorded on the withdrawal page of the CRF, or an SAE report will be completed if the subject has completed the study.

7.4 Investigational Products

7.4.1 Investigational Products Administered

A single injection of FX-322 or placebo will be administered on Day 1 by intratympanic injection. Subjects will be randomized to one of four treatment groups to receive a single dose of either FX-322L, placeboL, FX-322H, or placeboH. Randomized subjects are to be allocated 1:1 to each of 2 cohorts (12 in each cohort) and allocated 2:1 to study drug (8 FX-322:4 placebo) within each cohort. EMLA® topical anesthetic cream will be administered to the tympanic membrane using the provided applicator kit. The cream will cover the eardrum and remain in place for 2-3 minutes then suctioned clear. Under a microscope, a 25-gauge needle will be used to inject of 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 10-15 minutes. The injections will be performed at an appropriate location designated by a Board Certified Otolaryngologist trained and experienced in performing intratympanic injections.

7.4.2 Identity of Investigational Products

The investigational drug is FX-322 which is a fixed ratio dose combination of 2 small molecules: a glycogen synthase kinase (GSK) inhibitor (FX03) and valproate sodium (FX00),

a histone deacetylase (HDAC) inhibitor. FX-322 is in the form of a [redacted].

7.5 Preparation and Dispensing

The FX-322 investigational product is a sterile liquid for intratympanic injection only. FX-322 is prepared by mixing a diluent vial with a lyophilized active vial, which is stored refrigerated until use, within 6 hours of mixing.

An osmolarity matched placebo for FX-322 is a sterile liquid for intratympanic injection only. The placebo is prepared by mixing a diluent vial with a lyophilized vial, which is stored refrigerated until use, within 6 hours of mixing.

The components in the study drug and placebo are shown in the following tables:

Table FX-322 Study Drug:

Active Ingredients	[redacted]
FX03	[redacted]
Valproate Sodium	[redacted]
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The matched placebo has been developed with similar pH, osmolality and gelation as FX-322. In a 0.2 mL injection, placeboH contains [redacted]

Proposed Amounts of Active Agents to be Injected in Humans

	FX-322L **Total** (in a 0.05 mL injection)	**FX-322H** **Total** (in a 0.20 mL injection)
FX03	[redacted]	[redacted]
FX00	[redacted]	[redacted]

Frequency Therapeutics will supply sterile FX-322 and placebo, as a sealed sterile vial containing lyophilized ingredients and another sterile vial containing a diluent. The placebo or FX-322 is prepared by mixing a diluent vial with a lyophilized vial. Mixing is achieved by tapping the vial on the palm of the hand to wet the lyophilized cake. FX-322 and placebo are stored refrigerated until use, within 6 hours of mixing. Detailed instructions will be included with the vials and in the Pharmacy Manual.

7.5.1 Packaging and Labeling

For the injection, the study drug or placebo will be packaged in a sterile 1 mL tuberculin syringe with a sterile cap. The syringe will be labelled clearly with the details for each randomized patient. Two syringes per patient will be provided in case a back-up syringe is needed for injection. The low dose (0.05 mL) syringe will be filled to the 0.1 mL mark. The high dose (0.2 mL) will be filled to the 0.25 mL mark. The FX-322 and placebo preparations drawn into the syringes must be warmed in a heating unit. Refer to the Pharmacy Manual for further instructions.

7.5.2 Supply, Storage and Handling

The vials must be stored as indicated in the Pharmacy Manual. Empty vials and containers may be destroyed at the conclusion of the study, after the site monitor has performed accountability and in compliance with the site's SOP.

7.5.3 Compliance and Drug Accountability

Accountability for the study drug at the study site is the responsibility of the Investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. The otolaryngologist will complete a form post injection to note any complications or if any of the study treatment was not able to be administered. Where allowed, the Investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each subject, and return to Frequency Therapeutics (or destruction, if approved by Frequency Therapeutics) will be maintained by the clinical site. These records will adequately document that the subjects were provided the doses as specified in the protocol and should reconcile all study drug received from Frequency Therapeutics or its designee. Accountability records will include dates, quantities, batch/serial numbers, and subject identification numbers. The site monitor will review drug accountability at the site on an ongoing basis during monitoring visits.

7.5.4 Disposal, Return or Retention of Study Drug

All unused and used study drug will be retained at the site until inventoried by the site monitor. All used, unused or expired study drug will be returned to Frequency Therapeutics or if authorized, disposed of at the study site in accordance with governing regulations and documented.

7.6 Blinding and Un-blinding

7.6.1 Blinding

The subjects, all Frequency Therapeutics staff and representatives, investigators and site personnel will be blinded to the study drug assignment. The otolaryngologist may not be blinded to cohort assignment, but will be blinded to randomized treatment (FX-322 or placebo). The pharmacy staff who prepare the study drug will be unblinded and will not perform any other roles on the study other than drug preparation and accountability. The independent statistician and/or independent statistical programmer who is not otherwise involved with the study will generate the randomization schedule and will be un-blinded.

7.6.2 Un-blinding

Only in the case of emergency, when knowledge of the study drug administered is essential for the clinical management or welfare of the subject, may the Investigator un-blind a subject's treatment assignment. Under such conditions, the identity of the study drug will be obtained by contacting the CRO.
If possible, the Medical Monitor and Frequency Therapeutics should be consulted prior to breaking the blind. If the blind is broken for any reason, the Investigator must notify Frequency Therapeutics immediately of the un-blinding incident without revealing the subject's study treatment assignment to Frequency Therapeutics.
In the event that the treatment assignment is broken, the date, the signature of the person who broke the code and the reason for breaking the code must be recorded on the sourced documents. Any code-breaks that occur must be immediately reported to the Medical Monitor.
Any subject whose treatment assignment has been un-blinded will be followed up for safety purposes.
Each box will be labelled Study drug in compliance with applicable local regulations. FX-322, Placebo, and Diluent vials will be packaged in separate boxes.

Instructions on compounding the study drug will be provided in the pharmacy manual.

All study drug will be transported, received, stored and handled strictly in accordance with the product label, the instructions provided to the investigational sites, the sites standard operation procedures and applicable regulations.

7.6.3 Method of Assigning Subjects to Treatment Groups

Twenty-four subjects will be randomized to one of four treatment groups: FX-322L, placeboL, FX-322H, or placeboH. The allocation ratio to dose cohort will be 1:1, 12 subjects per dose cohort, and within each dose cohort the allocation ratio will be 2:1 (8 FX-322: 4 placebo). A permuted randomized block algorithm will be developed by an independent statistician and/or statistical programmer not otherwise involved in the study.
There will be no randomized stratification in this study.

7.6.4 Selection of Doses in the Study

The 2 doses proposed in this study, FX-322L and FX-322H will be dosed concurrently. In a previous human study, Study FX-322-103, we have demonstrated that a single dose FX-322H has been well tolerated in patients with hearing loss with no serious drug related adverse events. The only treatment-emergent adverse events occurring after intratympanic injection of study drug or placebo, but before cochlear implant surgery in Study FX-322-103 were transient ear pain, reported in both the active and placebo subjects, were most likely related to the intratympanic injection procedure. The systemic exposure to the drug in these patients was also very limited. Safety margins for plasma clinical maximal concentrations (C_{max}) for FX03 determined in this study range from 31 to > 4000-fold based on nonclinical systemic exposure in toxicity studies with Guinea Pig, Rat and Dog, while safety margins for plasma clinical C_{max} for FX00 were > 30-fold. FX00 is also approved in the US for the treatment of epilepsy and has been extensively studied in healthy volunteers and patients as both oral and intravenous formulations and has a well-characterized safety profile since its first approval in 1996. Further, valproate sodium C_{max} in the clinical PK study was 113 to 226-fold lower than

the accepted therapeutic range following systemic treatment for epilepsy (50-100 µg/mL; Depacon Prescribing Information, 1996).

While the highest proposed dose of FX-322 (with FX03 and FX00 as active ingredients) is considered well characterized for safety and tolerability with limited systemic exposure, we plan to also assess the safety and efficacy of a lower dose [redacted]. Based on these data, it is considered that assessing the lower dose concurrent to the higher dose is well justified and does not pose any additional risk.

7.6.5 Selection and Timing of Dose for Each Subject

Once a subject has been identified who meets all inclusion/exclusion criteria, the ear with the worse hearing will be selected, unless a rationale exists to treat the other ear. The Investigator will need to discuss that rationale with the Sponsor prior to randomization.

Each subject will be placed in the supine position. EMLA® topical anesthetic cream will be administered to the tympanic membrane using the provided applicator kit. The cream will cover the eardrum and remain in place for 2-3 minutes then suctioned clear. 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 10-15 minutes. The injections will be performed at an appropriate location designated by a Board Certified Otolaryngologist trained and experienced in administering intratympanic injections.

Subjects will be required to stay in the Phase 1 research unit overnight for observation, up to 28 hours post injection. Subjects will be given a choice of staying at the Phase 1 research unit the night before study drug injection.

7.6.6 Prior and Concomitant Therapy

At each study visit the study personal will question the subject about any medication taken, including vitamin supplements and herbal remedies. Any concurrent medications will be recorded in the subject's records and the eCRF. Any changes in doses or introduction of a new medication during the course of the study will be recorded.

7.6.7 Prohibited Medication/Therapy

Concomitant medications that are not allowed during the study are valproic acid (brand name (e.g. Depacon®, Depakote®, Depakene, Epival®, Valpro, and Epilim) or derivatives. Intratympanic injections of anything other than study medication are prohibited during the course of the study.

7.6.8 Rescue Medication

No rescue medication will be provided as no FDA approved treatment for sensorineural hearing loss exists. The Investigator should treat any adverse events as medically appropriate and per their standard of care. Investigators will discuss the need for oral steroids on an individual subject's basis with the Medical Monitor prior to prescribing the medication.

7.6.9 Treatment Compliance

Treatment will be given one time only by the investigator so subject treatment compliance will not be assessed.

8 TIMING OF STUDY PROCEDURES

Subjects will provide written informed consent before any study related procedures are performed.

The planned study assessments are in Section 7.1.2.

8.1 Pre-treatment

8.1.1 Screening Visit (Visit 1; Day -30 to 0)

- Obtain signed informed consent.
- Assess for eligibility (against the inclusion and exclusion criteria).
- Collect full medical history, including concomitant illnesses/diseases and concomitant medications.
- Record demographic data, such as ethnic origin, date of birth, and sex.
- Record historical disease data and diagnostic information (including prior audiogram for inclusion determination).
- Perform a physical examination, including body weight and height.
- Record vital signs (sitting blood pressure, body temperature, and heart rate).
- Perform a 12-lead ECG.
- Collect samples for hematology, coagulation, clinical chemistry, and urinalysis tests.
- Collect samples for hepatitis B surface antigen and hepatitis C antibody.
- Collect urine sample for pregnancy test, if applicable.
- Collect urine sample for drug screening (alcohol, cocaine, opiates, benzodiazepines, cannabinoids, barbiturates, and amphetamines).
- Perform otoscopy, comprehensive audiogram, word recognition testing, WIN testing, and tympanometry
- Each subject's audiogram will be sent to the Medical Monitor or back up designee for review and determination of final eligibility.

8.1.2 Baseline/Treatment Visit (Visit 2, Day 1)

The following procedures will be performed at the Baseline/Treatment Visit:

- Before injection of study drug:
    - Reassess for eligibility against the inclusion and exclusion criteria.
    - Up to 24 hours before study drug injection, perform a simple audiogram.
    - At least 30 minutes before study drug injection, 12 lead ECG will be recorded
    - Collect samples for hematology, coagulation, clinical chemistry, and urinalysis tests, and baseline serum sample for PK testing.
    - Collect concomitant medications.
    - Record vital signs.
    - Perform a urine pregnancy test, if applicable.
    - Perform otoscopy.

  - Record any changes in medical history that have occurred since the previous visit.
- When all the baseline procedures have been performed and the investigator has confirmed the subject's eligibility for the study, the subject will be randomized.
- Randomization will take place for eligible subjects, and each will receive an unique subject number.
- Inject FX-322 or placebo via intratympanic injection to the study ear.
- After study drug injection:
  - Collect serum samples for PK testing at the following time points: 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.

  - Record any adverse events that have occurred since study treatment.

8.1.3 Observation Visit (Visit 3, Day 2)

The Observation Visit (Visit 3) will take place 1 day after the Baseline/Treatment visit. The following procedures will be performed at the Observation Visit:

- Record any AEs that have occurred since the previous visit and any changes in concomitant medication.
- Record vital signs.
- Perform 12-lead ECG.
- Collect samples for hematology, coagulation, clinical chemistry, and urinalysis tests.
- Collect blood sample for biomarker analysis.
- Collect serum sample for PK testing at 24 hours (±4 hours) post injection.

8.1.4 Follow-up (Visit 4, [Day 15 ±3 days])

The Follow-up Visit (Visit 4) will take place at Day 15 (± 3 days). The following procedures will be performed at the Follow-up Visit:

- Record any AEs that have occurred since the last visit and any changes in concomitant medication.
- Perform interval noise history.
- Perform otoscopy, comprehensive audiogram, word recognition testing, WIN testing, and tympanometry.
- Record vital signs.
- Collect samples for hematology, coagulation, clinical chemistry, and urinalysis tests.
- Collect blood sample for biomarker analysis.
- Perform a urine pregnancy test, if applicable.

8.1.5 Follow-up (Visit 5 [Day 30±5 days], Visit 6 [Day 60±5 days], Visit 7 [Day 90±5 days])

The Follow-up Visits (Visits 5, 6, and 7) will take place 30, 60, and 90 ± 5 days after the Baseline/Treatment visit. The following procedures will be performed at the Follow-up Visits:

- Record any AEs that have occurred since the last visit and any changes in concomitant medication.
- Obtain interval noise history.
- Perform otoscopy, comprehensive audiogram, word recognition testing, WIN testing, and tympanometry.
- Record vital signs.
- Perform a urine pregnancy test, if applicable.
- Collect blood sample for biomarker analysis (at the Day 90 visit only)

8.2 Duration of Treatment

The duration of treatment will be 3 months plus 1 day.

9 SAFETY ASSESSMENTS

The planned schedule of assessments is in Section 7.1.2.

9.1 Safety Measurements Assessed

9.1.1 Concomitant Medication

Subjects will be asked about concomitant medications at time points outlined in the Table of Assessments. All concomitant medication information will be recorded in the CRF.

9.1.2 Clinical Laboratory Evaluation

The hematology and clinical chemistry laboratory analyses will be performed and used by the investigator to assess the laboratory data for clinical significance and pathological changes. The following laboratory safety tests will be performed at time points:

Hematology

- HEMOGLOBIN
- HEMATOCRIT
- WHITE BLOOD CELL (WBC) COUNT (TOTAL AND DIFFERENTIAL)
- RED BLOOD CELL (RBC) COUNT
- MEAN CELL VOLUME (MCV)
- MEAN CELL HEMOGLOBIN (MCH)
- PLATELET COUNT
- MCH CONCENTRATION (MCHC)

Coagulation

- PT
- APTT

Clinical Chemistry

- CREATININE
- UREA (OR BLOOD UREA NITROGEN [BUN])
- ASPARTATE TRANSFERASE (AST)
- ALANINE TRANSFERASE (ALT)
- GAMMA GLUTAMYL TRANSFERASE (GGT)
- ALKALINE PHOSPHATASE
- LACTATE DEHYDROGENASE (LDH)
- TOTAL BILIRUBIN
- ALBUMIN
- TOTAL PROTEIN
- SODIUM
- POTASSIUM
- CHLORIDE
- GLUCOSE
- URIC ACID
- TOTAL CHOLESTEROL
- TRIGLYCERIDES
- CALCIUM
- PHOSPHORUS

Urinalysis (random)

- PH
- GLUCOSE
- KETONES
- BLOOD
- PROTEIN
- MICROSCOPY

Urine drug screen (alcohol, cocaine, opiates, benzodiazepines, cannabinoids, barbiturates, and amphetamines) will be performed at Screening only.

Screening for hepatitis B surface antigen and hepatitis C antibody at Screening only.

Screening for pregnancy will be performed (urine β-HCG) as outlined in Table 1.

9.1.3 Vital Signs

Vital signs (temperature, blood pressure and heart rate) will be recorded at time points outlined in Table 1 and will be performed in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes.

9.1.4 Electrocardiogram

At Screening, prior to treatment at Day 1, and at Day 2, a 12-lead ECG will be performed. ECG tracings will be retained and labeled as per the standard procedures applicable to the clinical study site.

9.1.5 Physical Exam (PE)

A complete physical examination will be performed by a licensed physician at Screening.

Complete physical examinations include: general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes and any pertinent system based on any prior findings. Physical examinations may be performed at various unscheduled time points, if deemed necessary by the Investigator.

9.1.6 Body Mass Index (BMI)

BMI will be calculated by dividing the subject's body weight in kilograms by the subject's height in meters squared (BMI = kg/m^2). Body height (centimeter) and body weight (kilograms) will be measured at the time points delineated in the Schedule of Assessments. Body weight and height will be obtained with the subject's shoes and jacket or coat removed.

9.1.7 Noise Exposure

The subject will be queried about noise exposure since the last visit (Interval noise history) at Day 15, Day 30, Day 60, and Day 90 visits.

9.1.8 Otoscopy

Microscopic otoscopy will be included to specifically record any abnormalities of the external ear canal, tympanic membrane and middle ear and will be performed at Screening, prior to injection on Day 1 and at the Day 15, Day 30, Day 60, and 90 visits.

9.2 Audiometry

Refer to the Schedule of Assessments for timing and order of assessments.

9.2.1 Comprehensive audiogram

A comprehensive audiometric exam (a graphical representation) to determine how well a subject can hear as well as a person's ability to understand speech. will be performed at the Screening visit, prior to baseline, and Day 15, 30, 60, and 90. This will be performed on a calibrated audiometer by a licensed audiologist. At the is following different frequencies will be obtained: Air: 250 Hz, 500 Hz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz, and 8 kHz; Bone: 500 Hz, 1 kHz, 2 kHz, and 4 kHz.

9.2.2 Tympanometry

Tympanometry (an objective test of middle-ear function is an examination used to test the condition of the middle ear and mobility of the eardrum (tympanic membrane) and the conduction bones, by creating variations of air pressure in the ear canal. Middle ear compliance, peak pressure, and tympanogram type will be recorded. Tympanometry will be performed at the Screening, Day 15, 30, 60, and 90 Visits. The assessment will be performed by a licensed audiologist on a calibrated tympanometer. A print-out containing the tympanometry from the machine will be collected and store in the source document.

9.2.3 Word Recognition (quiet)

Word recognition in quiet (AB words) will be measured with recorded CNC word lists. The test will consist of 50 words presented to the subject and the percentage of words correctly identified will be recorded. Word recognition will be performed at Screening, Day 15, 30, 60, and 90 Visits. Testing will be performed at 40dB above speech reception threshold.

9.2.4 Words-In-Noise (WIN)

The Words-in-Noise Test (WIN) 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. The purpose of this test is to mimic the real world in which background noises are maintained at consistent levels for different listening situations. This test is conducted by presenting 2 lists of 35 recorded words to each ear. Overall accuracy will be recorded as the number of words identified correctly. This test will occur at Screening, Day 15, 30, 60, and 90. Testing will be performed at 40dB above speech reception threshold.

9.3 Pharmacokinetic Assessment

The systemic exposure of the active pharmaceutical ingredients will be assessed. Plasma levels of FX00 and FX03 will be measured from plasma samples obtained at time points according to **Table 1**. Calculated PK parameters include Cmax, $AUC0_{inf}$, CL, V_{ss}, $T_{1/2}$, and T_{max}.

10 ADVERSE EVENTS

Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the CRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs will be elicited by asking the subject a nonleading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?”. AEs should be reported on the appropriate page of the CRF.

Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

Mild:	An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities.
Moderate:	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
Severe:	An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug. Causality should be assessed using the categories presented in the following table:

Unrelated:	Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.
Unlikely:	Clinical event whose time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
Possible:	Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.

Probable: Clinical event with a reasonable time relationship to study drug administration and is unlikely to be attributed to concurrent disease or other drugs or chemicals.

Treatment Emergent Adverse Events (Audiometric and Otoscopic)

If any of the following criteria are met, the event will be recorded as an treatment emergent adverse event (TEAE) per ASHA guidelines (ASHA 1994):

- Asymmetric loss of hearing greater than 20 dB at any one frequency in the treated ear.
- Asymmetric loss of hearing greater than 10 dB at two adjacent frequencies in the treated ear.
- Asymmetric loss of response at three consecutive test frequencies where responses were previously obtained in the treated ear.

For word recognition testing, a follow up visit score that falls below the lower limit of the 95% confidence interval for the baseline word recognition score will be considered a TEAE (Thorton and Raffin 1978).

Additionally, if the subject experiences a perforation greater than 25% of the tympanic membrane in the treated ear this will be recorded as a TEAE.

If two subjects experience the same TEAE, randomization and dosing will be paused, data will be evaluated, and a determination will be made about dosing remaining subjects in the study.

Given that study participants are to be diagnosed with stable SNHL, there is the possibility that patients could be exposed to loud noise during the observation period of the study and before their scheduled audiometric testing. This noise exposure during could potentially contribute to the incidence of audiometric TEAEs and may complicate the interpretation of causality. For this reason, confirmation of audiometric TEAEs if observed, will be done at the subject's next study visit. Based on the repeat audiometric testing, the final interpretation of causality will be determined.

Action Taken

The investigator will describe the action taken in the appropriate section of the CRF, as follows:

- None
- Concomitant medication
- Other, specify.

Follow-up of Adverse Events

All investigators should follow up subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the CRF.

Documentation and Reporting of Adverse Events

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant CRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

10.1 Serious Adverse Events

Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non--worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the CRF).
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).
- Results in a congenital anomaly/birth defect.

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the Investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

Reporting of Serious Adverse Events

Any SAE must be reported by the Investigator if it occurs during the clinical study, whether or not the SAE is considered to be related to the investigational product. An SAE report consists of the SAE form, the AE form, and the concomitant medication form. A copy of these forms must be emailed **within 24 hours** for the attention of the Sponsor at [redacted]. Additional contact details of the Medical Monitor can be found in the Medical Monitoring Plan.

The Investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the study monitor.

The sponsor and/or CRO will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the independent ethics committee (IEC)/institutional review board (IRB) approval/favorable opinion of the study. In addition, CRO on behalf of the sponsor, will expedite the reporting to all concerned investigators, to the IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 7.3.4.

10.2 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (e.g. investigators brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

All suspected unexpected serious adverse reactions (SUSARs) will be the subject of expedited reporting. The sponsor and/CRO shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IRB within 7 days after knowledge by the sponsor of such a case and that relevant follow up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IRB within 15 days after knowledge by the sponsor of such a case. All investigators should follow up SUSARs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Post study SUSARs that occur after the subject has completed the clinical study must be reported by the investigator to the sponsor.

11 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

11.1.1 Descriptive Statistics

The study is a phase 1 / 2, randomized, double-blind, placebo-controlled single dose study to evaluate the safety at two dose levels of FX 322 (FX-322L and FX-322H) compared to placebo in adults with stable sensorineural hearing loss (no changes over 6 months of 10dB or more in any frequency). Approximately 24 subjects will participate in the trial. Subjects will be randomized to one of four treatment groups: FX-322L, placeboL, FX-322H, or

placeboH using a 1:1 allocation ratio for dose cohort (12 per cohort) and within each cohort a 2:1 allocation ratio for study drug (8 FX-322: 4 Placebo). Since the volume in the syringe may be potentially unblinding to the investigator, for this study cohort assignment may not be blinded to the otolaryngologist; however, randomization to FX-322 or placebo will remain double-blind. Following randomization subjects will receive a single intratympanic injection of blinded study drug into the "treated" or "study" ear. The contralateral ear will be designated as the "untreated" ear.

The primary objective(s) for this study is to assess the systemic safety of FX-322, the effect of FX-322 on otologic and audiologic measures, and the plasma PK profile to determine the systemic exposure to the active pharmaceutical ingredients. The statistical analyses will consist of descriptive statistics including the mean, standard deviation (SD), median, minimum and maximum statistics for continuous endpoints and numbers and percent for categorical endpoints. Statistics will be presented by dose cohort, treatment group, and overall. Where relevant, 95% confidence intervals for summary statistics will also be provided. Figures describing individual subject data may also be provided. The general statistical methods are outlined below; however, more detailed descriptions of the statistical methods and approaches will be provided in the Statistical Analysis Plan (SAP) which will be prepared and finalized prior to breaking the blind.

11.1.2 Sample Size

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.

11.1.3 Analysis Sets

For the purpose of analysis subjects will be considered participating in the study if they are randomized. Subjects signing the informed consent who are not randomized will not be included in any analysis.

- **Safety Analysis Set**

The safety analysis set will include all subjects exposed to study drug and will be analyzed according to the actual treatment received regardless of the randomized treatment. The safety analysis set will be used for safety analyses.

- **Pharmacokinetic Analysis Set**

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

- **Per Protocol Analysis Set (PPAS)**

The per protocol analysis set 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.

11.1.4 Subject Disposition

Subject disposition will be summarized by dose cohort, randomized treatment group, and overall and will include the following:

- The number of all randomized subjects regardless of exposure to study drug or availability of post-baseline data
- The number and percent of subjects in each analysis set
- The number and percent of subjects completing the study
- The number and percent of subjects not completing the study and the reason for early withdrawal

11.1.5 Description of Subgroups to be Analyzed

Give the small sample size it is not anticipated that the data will be summarized by subgroups other than treatment; however, analyses for some subgroups, if feasible, may be conducted.

11.1.6 Subject Demographics and Baseline Characteristics

Descriptive statistics for subject demographics and baseline disease status will be provided using the safety analysis set.

11.1.7 Safety Analyses

Safety will be evaluated using the safety analysis set and will include treatment emergent AEs (TEAEs), serious adverse events (SAE)s, vital signs, clinical laboratory measurements, electrocardiograms (ECGs), concomitant medications, otology and audiometry assessments. Summary descriptive statistics will be provided by actual treatment received and overall. No safety data will be imputed except for partial dates if required to determine if an adverse event is treatment emergent or a medication concomitant with exposure to study drug. Details of partial date imputation will be provided in the SAP.

11.1.7.1 Adverse Events

Treatment emergent adverse events (TEAEs) will be summarized via the MedDRA system by organ class and preferred term using subject incidence rates. Data will be tabulated by severity, physician assessment of relationship to study drug, serious TEAEs, and TEAEs leading to death or study withdrawal. Adverse events of the ear will also be summarized by treated vs. non-treated ear.

11.1.7.2 Clinical Laboratory Evaluations

The analysis of laboratory parameters will include descriptive statistics for baseline and each post-baseline visit along with the change from baseline and/or shift tables for the proportion of subjects within and outside the normal ranges. All laboratory assessments will be included in line listings. Urinalysis results will be presented in a similar manner as laboratory assessments. Pregnancy results will not be summarized but will be provided in data tables.

11.1.7.3 Vital Signs

Vital signs will be summarized via descriptive statistics similar to laboratory evaluations described above.

11.1.7.4 Physical Examination and Electrocardiogram

Baseline physical exam and electrocardiogram data, where relevant, will be summarized in the subject demographic and baseline characteristic table. All other physical examination and electrocardiogram data results will be provided in tables.

11.1.7.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded to identify the drug class and preferred drug name. Concomitant medications will include all medications that started, or were continuing, during or after administration of study drug. Prior medications will include all recorded medications that started and stopped prior to administration of study drug.
The number and percent of subjects using concomitant medications will be tabulated by drug class and preferred drug name. Prior medications will be presented in line listings only. Concomitant medications will also be provided in line listings.

11.1.7.6 Tympanometry and Otoscopy

Tympanometry and otoscopic results will be presented by dose cohort, treatment group and ear (treated vs. untreated) at baseline and each visit with changes and/or shifts from baseline.

11.1.7.7 Comprehensive Audiometry

Comprehensive audiometry will be summarized by frequency for each dose cohort, treatment group, and ear (treated vs. untreated) for baseline and each post-baseline visit including changes from baseline. Separate analyses will be conducted for air and bone.

11.2 Handling of Missing Data and Subject Withdrawals

In general, other than partial dates to assess treatment emergent AEs and concomitant medications, there will be no imputation of missing data. Subjects will be included in a particular analysis so long as they have no missing data for the particular endpoint and/or visit being evaluated.

11.3 Protocol Deviations

Protocol deviations will be provided in line listings. A table of major and minor protocol deviations will be tabulated by dose cohort, treatment group, and overall.

12 QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

12.2 Monitoring

Data for each subject will be recorded on a eCRF. Data collection must be completed for each subject who signs an informed consent form (ICF) and is administered study drug.

In accordance with GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable.

The investigator must permit the monitor, the IEC/IRB, the sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

12.3 Data Management and Coding

The sponsor or CRO will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures (SOPs) of the data management and biostatistics departments of sponsor or CRO.

Study centers will enter data directly into an electronic data capture (EDC) system by completing the CRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and WHO Drug for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

13 RECORDS AND SUPPLIES

13.1 Drug Accountability

On receipt of the study drug, the investigator (or deputy) will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts before completing a supplies receipt. The investigator will retain a copy of this receipt at the study center and return the original receipt to the study monitor. The monitor may check the study supplies at each study center at any time during the study.

It is the responsibility of the study monitor to ensure that the investigator (or deputy) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will arrange collection of unused study drug returned by the subject. The study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

13.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between CRO and the sponsor.

14 ETHICS

14.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

14.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

14.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

14.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, potential risks, and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or their authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of

benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent will be obtained.

14.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the United States (US) FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act (1), applicable to national and/or local laws and regulations on personal data protection.

Reporting and Publication, Including Archiving

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

15 REFERENCES

1. US Department of Health and Human Services. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 (P.L.104-191) [HIPAA]. http://aspe.hhs.gov/admnsimp/pl104191.htm. Effective August 21, 1996.
2. Li, L., Chao, T., Brant, J., O'Malley Jr, B., Tsourkas, A., & Li, D. (2017). Advances in Nano-based inner ear delivery systems for the treatment of sensorineural hearing loss. Adv Drug Delivery. Advanced Drug Delivery Reviews.
3. Hong , O., Kerr, M., & Poling , G. (April, 2013). Understanding and preventing noise-induced hearing loss. ELSEVIER, 110-118.
4. Basner, M., Brink, M., Bristow, A., de Kluezinaar, Y., Finegold , L., & Hong, J. (2015). ICBEN review of research on the biological effects of noise 2011-2014. Noise & Health, 57-82.
5. Lin, F., Niparko, J., & Ferrucci, L. (November, 2011). Hearing loss prevalence in the United States. Arch Intern Med., 1851-1853.
6. Nelson DI, Nelson RY, Concha-Barrientos M, Fingerhut M, (2005). The global burden of occupational noise-induced hearing loss. Am J Ind Med, 48(6): 446-458.
7. Choi, J., Betz, J., Li, L., Blake, C., Sung, Y., Contrera, K., & Lin, F. (July 2016). Association of Using Hearing Aids or Cochlear Implants With Changes in Depressive Symptoms in Older Adults. JAMA Orolaryngology -Head & Neck Surgery, 142(7):652–657.
8. McGilton, K., Höbler, F., Campos, J., Dupuis, K., Labreche, T., & Guthrie, D. (2016). Hearing and vision screening tools for long-term care residents with dementia: protocol for a scoping review. BMJ Open.
9. Deal, J., Betz, J., Yaffe, K., Harris, T., Purchase-Helzner, E., Satterfield, S., & Pratt, S. (2017). Hearing impairment and incident dementia and cognitive decline in older adults: The health ABC study. Journals of Gerontology - Series A Biological Sciences and Medical Sciences, 703-709.
10. Thornton AR, Raffin MJM: Speech discrimination scores modified as a binomial variable. *J Sp Hear Res* 1978;21:507–518.
11. American Speech-Language-Hearing Association. (1994). Guidelines for the audiologic management of individuals receiving cochleotoxic drug therapy. ASHA 36 (Suppl 12):11-19.
12. World Health Organization. (2015). Hearing Loss due to recreational exposure to loud sounds: A review.
13. 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.

16 APPENDIX 1

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.

17 INVESTIGATOR SIGNATURE PAGE

Protocol Title: 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

Confidentiality and GCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Frequency Therapeutics and of the IRB. I will submit the protocol amendments and/or any ICF modifications to Frequency Therapeutics and IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all CRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by [sponsor name], to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution