Statistical Analysis Plan:

Sponsor Name: Pipeline Therapeutics, Inc.

Protocol Number: PTI-505-101

Protocol Title: A Phase I/IIa, Randomized, Double-Blind, Placebo-Controlled, Safety, Pharmacokinetic, and Preliminary Efficacy Study of Unilateral Intratympanic PIPE-505 in Subjects with Sensorineural Hearing Loss Associated with Speech-in-Noise Impairment

Protocol Version and Date: Amendment 3 V4.0 (18-Sep-2020)

IND #: 144418

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[redacted]

1. Glossary of Abbreviations

[redacted]	[redacted]
AE	Adverse event
ANF	Auditory nerve fiber
AP	Action potential
AUC	Area under the curve
BMI	Body mass index
CL/F	Apparent clearance
Cmax	Maximum plasma concentration
CS	Cochlear synaptopathy
daPa	DekaPascals
dB	Decibel
DMC	Data Monitoring Committee
[redacted]	[redacted]
ECG	Electrocardiogram
[redacted]	[redacted]
FAS	Full analysis set
FDA	Food and Drug Administration
FOCP	Females of child-bearing potential
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HCG	Human chorionic gonadotropin
HHL	Hidden-hearing-loss
Hz	Hertz
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MMRM	Mixed model with repeated measurements
[redacted]	[redacted]
PI	Principal Investigator
PK	Pharmacokinetic
QTcF	Fridericia's Correction Formula
[redacted]	[redacted]
SNHL	Sensorineural Hearing Loss
SNR	Signal-to-noise ratio

SR	Spontaneous rate
[redacted]	[redacted]
[redacted]	[redacted]
t½	Apparent terminal-phase disposition half-life
TEAE	Treatment-emergent adverse
tmax	Time to maximum plasma concentration
TM	Tympanic membrane
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Vz/F	Apparent volume of distribution

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

[redacted] will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings. Pharmacokinetic (PK) analyses will be carried out by [redacted], and the details of analysis are provided in Section 9 of this SAP.

2.2. Timings of Analyses

The primary analysis of the safety and tolerability profile of PIPE-505, and secondary and exploratory preliminary efficacy endpoints will be performed up to 3 months following a single unilateral intratympanic injection after all subjects complete the Day 90 visit or terminate early from the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock. There is no planned interim analysis in this study.

An independent Data Monitoring Committee (DMC), will review accumulating safety data periodically during the study. Blinded listings will be provided to the DMC and an independent unblinded statistician from [redacted] will be available to provide treatment information to DMC members upon request. DMC procedures and the list of blinded listings are outlined in the DMC charter.

A blinded ad hoc analysis may be performed upon sponsor's request during the study. The scope of the ad hoc analysis will include, but not limited to, the blinded listings to be provided to the DMC with the addition of [redacted]

3. Study Objectives

3.1. Primary Objective

The primary objective is to assess the safety and tolerability profile of PIPE-505 when administered as a single unilateral intratympanic injection.

3.2. Secondary Objective

The secondary objective is to assess the single dose plasma PK profile of PIPE-505 following a single unilateral intratympanic injection.

3.3. Exploratory Objectives

The exploratory objectives are:

1. [redacted]

[redacted]

[redacted].

3.4. Brief Description

This is a Phase I/IIa, randomized, double-blind, placebo-controlled, single dose study in subjects with sensorineural hearing loss (SNHL) associated [redacted]

[redacted]

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

[redacted] This study plans to enroll subjects at approximately 7 sites in the US. Additional site(s) may be recruited to ensure the timely enrollment of study subjects.

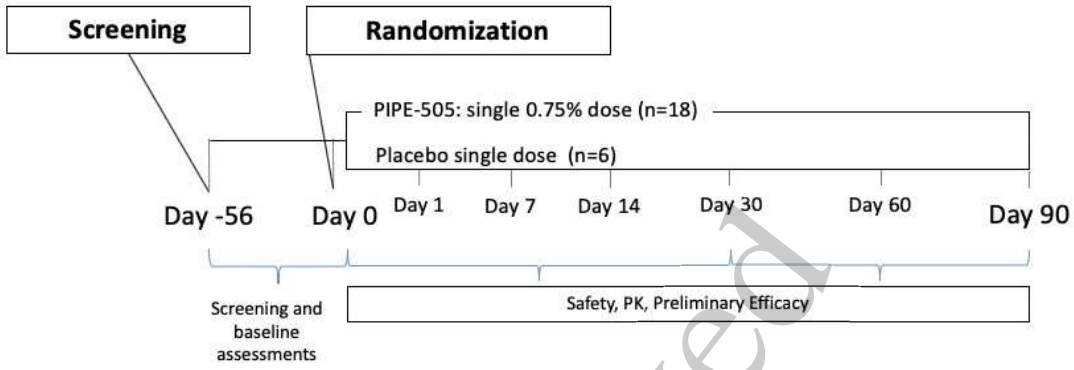
The total duration of subject participation is up to [redacted]:

- [redacted]

- [redacted]

[redacted]

[redacted]



3.5. Subject Selection

Subjects will be screened for eligibility based on the following inclusion and exclusion criteria.

3.5.1. Inclusion Criteria

Subjects must meet each of the following inclusion criteria to be eligible for randomization:

1. Ability to personally provide written, signed, and dated informed consent to participate in the study.

2. Subject's primary language is English.

3. Male or female between 18 and 75 years of age, inclusive, at randomization.

4. [redacted]

5. [redacted]

[redacted]

7. Male or female subjects with reproductive potential agree to comply with approved double barrier contraceptive method (e.g., condom plus intrauterine device [IUD], condom plus hormonal contraception, or double barrier method, i.e., condoms and diaphragms with spermicidal gel or foam) during and for 3 months after study drug administration.

Subjects are considered of non-reproductive potential if:

a. Post-menopausal female with ≥12 consecutive months of spontaneous amenorrhea and age ≥51 years with follicle-stimulating hormone (FSH) >30 mIU/mL at Screening

b. Surgically sterile female and at least 6 weeks post-sterilization (i.e., bilateral oophorectomy or hysterectomy)

c. Sterilized male at least 1-year post vasectomy and confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

8. The subject is in general good medical health with no clinically significant or relevant abnormalities, including medical history, physical exam, vital signs, electrocardiogram (ECG), and laboratory evaluations (hematology, chemistry, and urinalysis) as assessed by the Investigator.

9. An understanding, ability, and willingness to fully comply with study procedures and restrictions.

3.5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. [redacted]

2. History of chronic otitis externa or media, other chronic middle ear disorders, or perilymph fistula.

3. Presence of a genetic, syndromal or developmental auditory disorder.

4. Presence of an autoimmune or serious neurological disorder that could contribute to auditory loss, as determined by the Investigator.

5. History of herpes zoster oticus, or other infectious etiology of hearing loss as determined by the Investigator.

6. History of barotrauma as determined by the Investigator.

7. [redacted]

8. [redacted]

9. Any prior exposure to platinum-based medications.

10. Otological disorders that would preclude safe tympanic injection (e.g., history or presence of cholesteatoma, tympanic membrane (TM) perforation, otitis media, or middle ear anatomic anomaly) as determined by the Investigator.

11. Presence of a cochlear implant.

12. History of Meniere's disease or endolymphatic hydrops.

13. History of bothersome tinnitus, as determined by the Investigator.

14. Past otologic surgical procedures that would preclude safe, intratympanic injection as determined by the Investigator.

15. Intratympanic injection within 6 months of randomization.

16. Use of an investigational product or intervention other than a non-interventional registry study (including vaccine studies) within the greater of 30 days or 5 half-lives (if known) prior to Screening or expected during the study.

17. [redacted]

18. History of malignancy under current active treatment or considered at substantial risk for progression or recurrence during the study interval, as determined by the Investigator. Note, central nervous system neoplasms or head and neck cancer are excluded from eligibility regardless of treatment status.

19. The subject has a QTcF by ECG >450 milliseconds for males or >470 milliseconds for females.

20. The subject has a history of dysrhythmia (such as atrial fibrillation or ventricular tachycardia, etc.) that is considered unstable by the Investigator.

21. The subject has experienced a significant systemic illness, as judged by the Investigator, within 30 days prior to Screening.

22. The subject has a current or relevant history of physical or psychiatric illness, or any medical disorder that may require treatment or make the subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedure, as determined by the Investigator.

23. Known or suspected intolerance or hypersensitivity to the investigational product or closely-related compounds.

24. The subject is pregnant or breastfeeding or plans to become pregnant during the study.

25. History of alcohol or other substance abuse within 6 months of Screening as determined by the Investigator.

26. Subject is Hepatitis B positive (Subjects who are surface antibody positive secondary to immunization are eligible).

27. History of Hepatitis C.

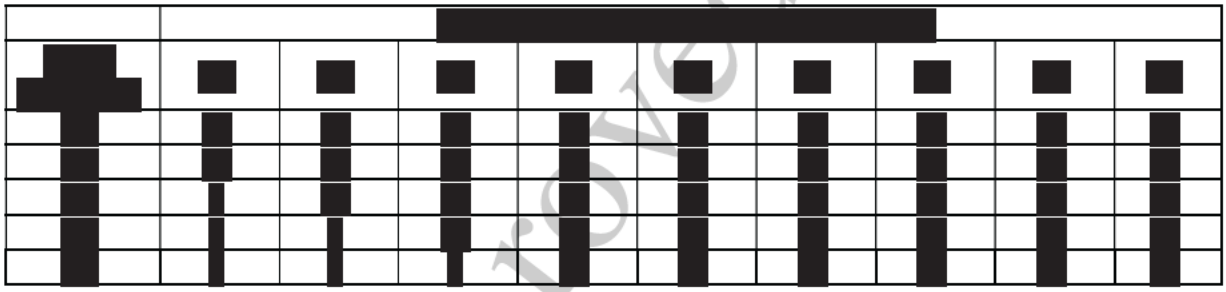
28. Subject is Human Immunodeficiency Virus (HIV) seropositive.

3.6. Determination of Sample Size

No formal sample size calculation was performed. The sample size of this study is not based on statistical considerations. A sample size of 24 subjects (18:6 PIPE-505:Placebo) is considered sufficient to characterize the initial safety, tolerability, single dose PK profiles, and exploratory preliminary efficacy endpoints as measured by clinical, behavioral, and electrophysiological responses.

[redacted]

Table 1. Estimated Total Sample Size Per Treatment Group Needed to Detect QuickSIN-EP Mean Difference and Standard Deviation Combinations with 80% Power, a=0.05, 2-sided, and 3:1 Allocation of Study Drug to Placebo



[redacted]

3.7. Treatment Assignment and Blinding

All eligible subjects will be randomly assigned to treatment (PIPE-505 or Placebo), based on the randomization schedule (a computer-generated randomization list) produced by an independent unblinded biostatistician from [redacted].

The randomization schedule will be generated and loaded to the Interactive Voice/Web Response System (IxRS) prior to the start of the study. [redacted]

An unblinded dose preparer will:

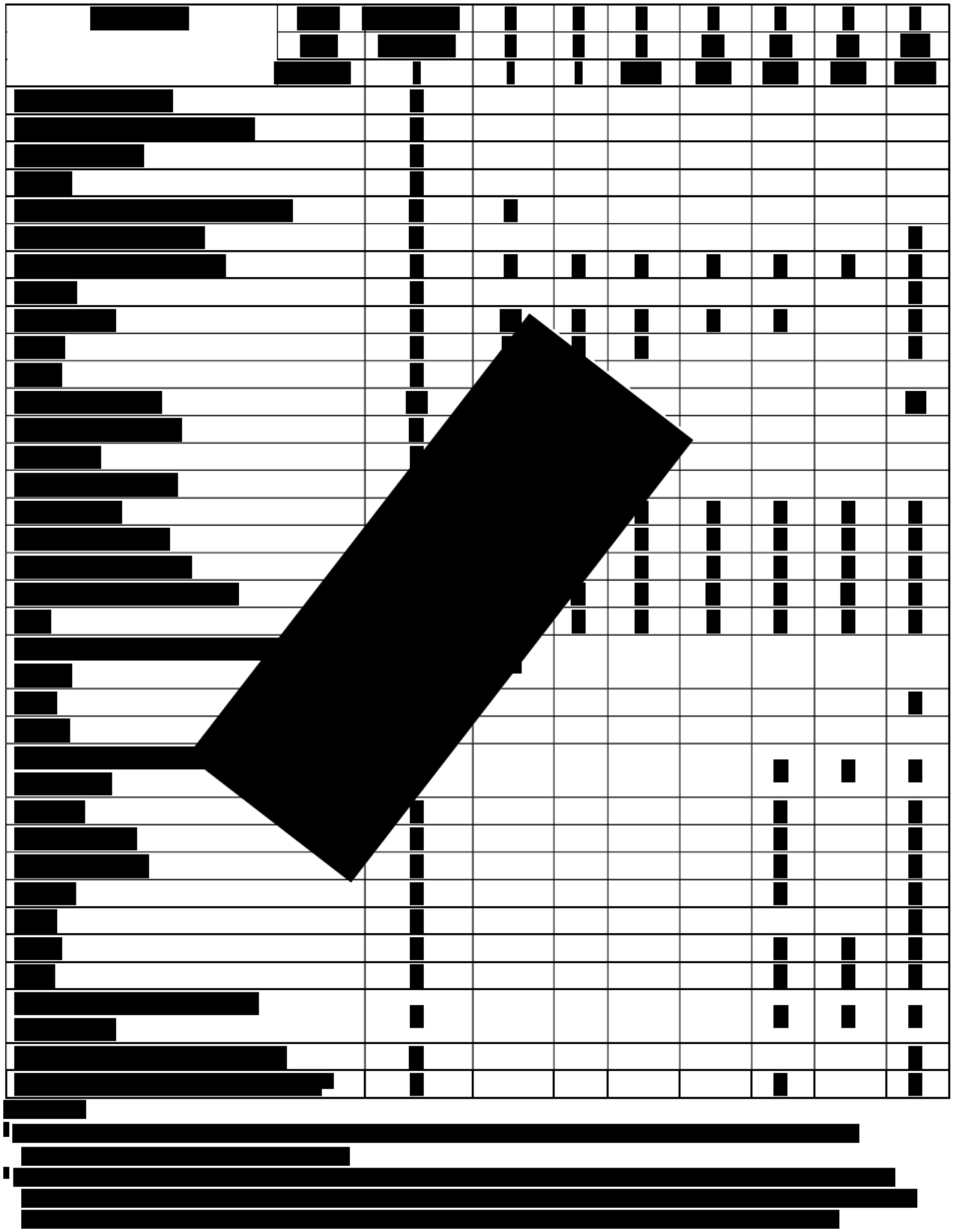
- Be responsible for preparing the study dose of PIPE-505 or Placebo according to the randomization assignment (kit number) obtained through the IxRS

- Deliver the preloaded syringe to the unblinded otologist or neuro-otologist [redacted]
- Be identified on the site delegation of responsibility log as the unblinded dose preparer.
- Be restricted from participating in any subject assessment
- Be restricted from disclosing treatment assignments to any study staff, with the exception of otologist/neuro-otologist who administers study drug.

3.8. Administration of Study Medication

[redacted]

3.9. Study Procedures and Flowchart



[redacted] speaker.

[redacted]

4. Endpoints

4.1. Primary Endpoint

The primary endpoint of the study is the number and severity of adverse events (AEs) up to 3 months following a single unilateral intratympanic injection of PIPE-505.

4.2. Secondary Endpoint

The secondary endpoint of the study is the single dose plasma PK parameters of PIPE-505, including AUC_t, AUC_{24}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{½}$, CL/F, Vz/F, λz (see SAP Section 9.1 for definitions).

4.3. Exploratory Endpoints

[redacted]

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

5. Analysis Sets

5.1. Enrolled Set

[redacted]

5.2. Randomized Set

[redacted].

5.3. Safety Analysis Set

Safety Analysis Set includes all randomized subjects who received the study medication. Subjects will be analyzed according to treatment received. The Safety Analysis Set will be used for primary analysis and all safety analyses.

5.4. Full Analysis Set

[redacted]

5.5. Per-Protocol Set

[redacted]

[redacted]

5.6. Pharmacokinetic Set

The PK Set includes subjects in the Safety Analysis Set who have no major deviations related to IP intake and have at least one quantifiable post-dose PK sample available. The PK Set will be used for PK analysis.

6. General Aspects for Statistical Analysis

6.1. General Methods

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

6.2. Key Definitions

6.2.1. Baseline

Baseline will be defined as the last assessment done before study medication administration (considering unscheduled visits when available). Change from Baseline will be defined as the measurement at each time point minus the Baseline value.

6.2.2. Study Day

Study Day is calculated relative to the date of study drug administration. Day 0 is defined as the study medication administration day.

6.2.3. End of Study

A subject is considered to have fulfilled the requirements for study completion if/when the subject has completed all study periods and Visit 7 ([redacted]

The scheduled End of Study/Early Termination will be the last subject's visit at Visit 7.

6.3. Missing Data

6.3.1. Birth Dates

If the date of birth is only partially available, the first of the month will be imputed for any missing days and January will be imputed for any missing months. Imputed dates will not be presented in the data listings.

6.3.2. Medication/Procedure Dates

For prior and concomitant medications/procedures with incomplete dates, the following rules will be used to impute start and/or stop dates for the purposes of determining if a medication is prior or concomitant only. Imputed dates will not be presented in the data listings.

For partial start dates:

- If day is missing, and the month and year match the month and the year of the study medication administration date, the day of the study medication administration date will be imputed. Otherwise, the first of the month will be used.
- If day and month are missing and the year matches the year of the study medication administration date, the month and the day of the study medication administration date will be imputed. Otherwise, January 1st will be used.
- If the start date is completely missing, and the stop date is on or after study medication administration date, the start date should be imputed as the administration date and the medication will be considered concomitant medication. If the start date is completely missing and the stop date is before the study medication administration date, the medication will be considered to be prior only.
- If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date.

For partial stop dates:

- If the day is missing, then the last day of the month will be used.
- If the month is missing, then December will be used.
- If the stop date is completely missing then the date of last study visit will be used.

If the start date for a medication is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

6.3.3. Adverse Events

For AEs with incomplete dates, the following rules will be used to impute start and/or stop dates for the sole purpose of determining if an AE is treatment-emergent. Imputed dates will not appear in the data listings.

For partial start dates:

- If day is missing, and the month and year match the month and the year of the study medication administration date, the day of the study medication administration date will be imputed and the AE will be considered treatment-emergent. Otherwise, the first of the month will be used and the treatment-emergent status will be assessed relative to the study medication administration date.

[redacted]

- If the day and month are missing, and the year matches the year of the study medication administration date, the month and the day of the study medication administration date will be imputed, and the AE will be considered treatment-emergent. Otherwise, January will be used and the treatment-emergent status will be assessed relative to the study medication administration date.

- If the start date is completely missing, the AE will be considered treatment-emergent unless the stop date is complete and prior to the study medication administration or provides enough partial information to rule out a treatment-emergent status.

- If the stop date is complete and the imputed start date is after the actual stop date, then the start date will be imputed as the stop date and the treatment-emergent status will be assessed relative to the study medication administration date.

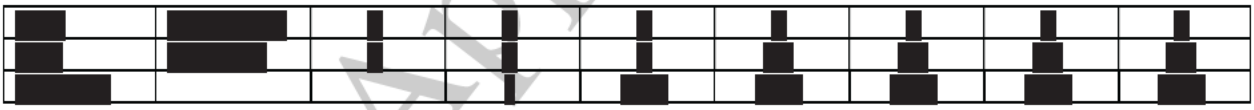
Any missing severity assessments for AEs will be imputed as "severe" and any missing relationship to study medication or study procedure will be considered "related" for summary purposes.

6.4. Visit Windows

All data will be summarized according to the scheduled visits and time points as outlined in the Protocol Amendment 3, Version 4.0 and by the visit denoted on the electronic case report form (eCRF). If there are multiple scheduled visits for the same visit window, the last scheduled visit will be chosen for the summary tables.

Subjects who discontinue early will be encouraged to return to the site to complete early termination assessments for safety purposes. Early termination procedures should follow the Day 90 schedule. End of Study/Early termination visit will be mapped to the closest scheduled visit based on study day for analysis purposes. All visits including unscheduled visits and time points will be listed.

The study scheduled visits



6.5. Pooling of Centers

Not applicable.

6.6. Subgroups

No subgroup analysis is planned for this study.

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Discontinuation

A summary of subject disposition will be provided for the number of subjects screened, number of screen failures and reasons for screen failures, as well as the number of subjects in each analysis set (Enrolled Set, Randomized Set, Safety Analysis Set, Full Analysis Set, Per-Protocol Set, and PK Set). In addition, the number and percent of subjects in each of the following categories will be provided:

- Subjects who complete the study
- Subjects who discontinue early from study
- Reasons for early discontinuation from the study

Subject disposition information will be provided overall and by treatment group.

The number of subjects in each analysis set will also be summarized.

A separate summary will be provided for the number and percentage of subjects attending each visit. Percentages will be based on the Safety Analysis Set.

7.2. Inclusion/Exclusion Criteria

Inclusion/exclusion criteria definitions and violations will be listed. Subjects with inclusion criteria not met or exclusion criteria met will be reported.

7.3. Protocol Deviation

Protocol deviations are pre-defined in the study. Deviations will be categorized as major or minor. Major protocol deviations will be summarized by category using the Randomized Set.

7.4. Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented overall and by treatment group for the Safety Analysis Set and Full Analysis Set.

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) for age, height, weight, and body mass index (BMI) will be summarized by treatment group and overall. Distribution of subjects by sex, race, ethnicity, and child-bearing potential (Yes/No) will be summarized overall and by treatment group. Following conversions will be applied where appropriate.

- Weight (in kg) = weight (in lbs) * 0.4536.
- Height (in cm) = height (in inch) *2.54
- BMI = Weight(kg) / (Height(m)^2)

7.5. Medical History and Audiological/Otological History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.1, summarized and presented overall and by treatment group based on the Safety Analysis Set. Summaries will be ordered alphabetically by system organ class (SOC) and then, within a SOC, alphabetically by preferred term (PT).

Audiological/Otological history including SNHL will be coded and summarized using MedDRA version 22.1

[redacted]

for the Safety Analysis Set. Categorical summary of audiological/ontological history will be provided.

Medical history and Audiological/Otological history will be provided separately in separate listings.

7.6. Other Baseline Characteristics

[redacted]

7.7. Prior and Concomitant Medication/Procedures

Medications will be coded using World Health Organization Drug Dictionary (WHO-DD) March 2020 B3. Prior and concomitant medications/procedures will be summarized separately by presenting the counts and percentage of subjects using medications overall and by each treatment group in the Safety Analysis Set. Summaries will be provided by Anatomical Therapeutic Chemical (ATC) classification Level 2 term and PT. Medication summaries will be sorted alphabetically by ATC Level 2 and then by PT within each ATC Level 4. Subjects will be counted only once for each medication class and each preferred drug name.

7.7.1. Prior Medication

Prior medications will be presented in a summary table overall and by treatment group. Any medications (including herbal treatments, vitamins, non-pharmacological treatment such as psychotherapy as appropriate) received within 30 days prior to signing the Informed Consent Form (ICF) are considered as prior.

Missing date imputation rules are provided in Section 6.3.2.

7.7.2. Concomitant Medication

Concomitant medications will be presented in a summary table similarly to prior medications. Concomitant medication is defined as any medication taken from the date of signing the ICF through the [redacted]y follow-up visit.

Missing date imputation rules are provided in Section 6.3.2.

7.7.3. Concomitant Procedure

Concomitant procedure is defined as any procedure operated on or after the study medication administration date through the [redacted] follow-up visit. Concomitant procedures will be presented in a listing.

Missing date imputation rules are provided in Section 6.3.2.

8. Efficacy Analysis

8.1. Exploratory Efficacy Endpoints

[redacted]

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

8.1.1. [redacted]

[redacted]

8.1.2. [redacted]

[redacted]

8.1.3. [redacted]

[redacted]

[redacted]

8.1.4. [redacted]

[redacted]

8.1.5. [redacted]

[redacted]

8.1.6. [redacted]

[redacted].

8.1.7. [redacted]

[redacted]

8.1.8. [redacted]

[redacted]

[redacted].

8.1.9. [redacted]

[redacted]

[redacted]

[redacted]

8.1.10. [redacted]

[redacted]

8.1.11. [redacted]

[redacted]

8.1.12. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9. Analysis of Pharmacokinetics

The blood samples will be collected pre and post dose as shown in the time and events schedule in Section 3.9. [redacted]

9.1. PK parameters

PK parameters of PIPE-505 will be derived using non-compartmental analysis methods from the concentration-time data for all evaluable subjects using a validated Phoenix WinNonlin software version 8 or higher. Actual sampling times, rather than scheduled sampling times will be used in all computations involving sampling times. Table below describes the PK parameters that will be determined from concentrations of PIPE-505 in plasma.

Plasma PK Parameters for Analysis

Parameter	Definition
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_{\infty}=AUC_t+C_{last}/\lambda z$, where C_{last} is the last quantifiable concentration.
AUC_{24}	Area under the plasma concentration-time curve from time 0 to 24 hours, calculated using the linear trapezoidal rule.
C_{max}	Maximum observed plasma concentration.
CL/F	Apparent clearance after extravascular administration, calculated as Dose/AUC_{∞} after a single dose.
λz	Terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase.
$t_{1/2z}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda z$.
t_{max}	Time to reach C_{max}.
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda z$.

9.2. Handling of missing and Below Limit of Quantification (BLQ) data

Missing concentration data for all patients who received scheduled study treatments will be considered as non-informative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the derivation of PK parameters and for the individual plasma concentration versus time curves, the

following rules will apply:

- Concentration values below the assay's lower limit of quantification (BLQ) in pre-dose Day 0 samples will be treated as zero;
- The sampling time of pre-dose samples relative to dosing will also be treated as zero;
- All BLQ values occurring after dose will be set to missing.

For plasma concentration summary, the following rules will apply:

- All BLQ values will be set to zero.

9.3. Individual PK Data

The actual and nominal sampling times of PK blood sample collection will be listed for each patient and will include the deviation in time from the protocol scheduled time (i.e., nominal time), if applicable.

The individual plasma concentration versus time profiles using the actual sampling time will be presented for the given treatment.

9.4. Summary of PK Data

The plasma concentration data will be summarized by day/time point for the given treatment.

The PK parameters will be summarized for PIPE-505 group.

[redacted]

10. Safety Analysis

All the safety endpoints will be summarized using Safety Analysis Set. All AEs will be coded using MedDRA version 22.1.

10.1. Study Drug Administration

A listing of study drug administration will be provided for the Safety Analysis Set. The listing will include the ear, the medication injected, date and time, and the volume of drug administration.

10.2. Adverse Events

The number of events, incidence, and percentage of treatment-emergent AEs (TEAE) will be calculated overall and by treatment group.

- Overall TEAEs
- Serious TEAEs
- Study Drug Related TEAE
- Study Drug Related Serious TEAE
- Study Procedure Related TEAE
- Study Procedure Related Serious TEAE
- TEAE by SOC and PT
- TEAE by SOC and PT, and Maximum Severity
- TEAE leading to Study Discontinuation
- TEAE leading to Death

Selected tables will be presented by SOC and by PT. Events with missing onset dates and end date after the study drug exposure or missing will be included as treatment-emergent. TEAEs are considered those events occurring or worsening with onset dates on or after study drug exposure through end of study (Day 90). If a subject experiences more than one occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be summarized. The missing severity will be considered as “severe”. TEAEs will be further summarized by severity and relationship to study drug. AE listings will be presented.

10.3. Clinical Laboratory Tests

Clinical laboratory tests will be summarized by treatment group and visits. Change from baseline values will be summarized and shift tables will also be presented separately.

Laboratory results collected in conventional units will be converted to International System of Units (SI) for all summaries and listings. Clinical laboratory test results (hematology, serum chemistry) and their changes from baseline will be summarized by visit and treatment group using descriptive statistics. Shift tables for hematology and chemistry using categories of low, normal, and high, comparing laboratory test results from Baseline to each visit will be presented with percentages based on subjects with a non-missing value at baseline and post-baseline visit. Urinalysis laboratory tests will be listed only as it is collected at screening only.

The laboratory tests including pregnancy test results and potentially clinical important findings will be

[redacted]

provided in a listing. Coagulation panel and other tests will be added in the listings. Serum pregnancy, urine pregnancy, FSH, Hepatitis B, Hepatitis C, and HIV tests are performed as other tests; and both coagulation panel and other tests will be included in the listings.

10.4. Vital Signs

Vital signs (body temperature, respiration rate, pulse rate, systolic and diastolic blood pressure measurements, and body weight) are evaluated at the visits. Body weight (without shoes) will be recorded whenever vital signs are recorded; height (without shoes) will be recorded at Screening only.

Vital signs results will be summarized and presented in a listing.

The following conversion factor will be used to convert any temperatures reported in degrees Fahrenheit to Celsius:

Temperature (in °C) = 5/9 (Temperature [in °F]-32).

10.5. Physical Examination

Complete physical examinations, per each institution's guidelines, will be performed at Screening and end of study, and involves the following body system: general appearance; head, neck, eyes, nose and throat; respiratory; cardiovascular; abdomen (gastrointestinal); skin; genitourinary system; lymph nodes; musculoskeletal; neurological; and other. Any abnormal change from the baseline physical examination assessment must be assessed as not clinically significant (NCS) or clinically significant (CS) by the Investigator and recorded in the source document and eCRF. Any clinically significant change or new diagnosis as a result of a clinically significant change, as determined by the Investigator, will be recorded as an AE in the source documentation.

Physical examination results will be provided in a listing only.

10.6. Otological Examination

The otologic examination will include direct examination of the external ear, ear canal, and TM by otoscope, as well as standard testing of tympanic mobility. The otological examinations will be conducted by the unblinded otologist or neuro-otologist who performs the intratympanic injection and also conducts all post-injection otological examinations through at least Day [redacted], and preferably throughout the study.

Otological examination listing will be provided. Examination date, otological examination is performed (Yes/No), results of each test, and any detailed information for abnormal results will be presented in the listing.

10.7. Electrocardiograms

Standard 12-lead ECGs will be recorded at Screening, Visit 1, Visit 2, Visit 3, and Visit 7. The Visit 1 (Day 0) ECG will only be conducted at 4 hours (±15 minutes) post-dose. The ECG at Screening may be repeated at the Investigator's discretion to confirm the QTcF result. ECG parameters will be evaluated for Heart Rate (bpm), PR Interval (msec), RR Interval (msec), QT Interval (msec) Fixed, QRS Interval (msec), and QTcF Interval (msec). Descriptive statistics and change from baseline will be summarized and the listing will be provided. ECG evaluation will be recorded as normal or abnormal on the eCRF and all abnormal results will be evaluated as Normal, Abnormal NCS or Abnormal CS. ECG evaluation shift from baseline table will be provided.

10.8. Tympanometry

Tympanometry assesses the relationship between the air pressure in the ear canal and the movement of the TM. The test measures the compliance of the TM to changes in air pressure, as well as reflex contraction of the middle ear muscles. [redacted]

11. Interim Analyses

There are no planned interim analyses.

[redacted]

12. Changes from Analysis Planned in Protocol

None.

[redacted]

13. Reference List

[redacted]

14. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

14.1. General Considerations

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in RTF format or portable document format (pdf).
- Numbering of TFLs will follow ICH E3 guidance

14.2. Table, Listing, and Figure Format

14.2.1. General

- All TFLs will be produced in landscape format.
- All TFLs will be produced using the Courier New font, size 8.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color).
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used.
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.2.2. Headers

- All output should have the following header at the top left of each page:
- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

[redacted]

- The date output was generated should appear along with the program name as a footer on each page.

14.2.3. Display Titles

- Each TFL should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination. A decimal system (x.y and x.y.z) is used to identify TFLs with related contents. The title is centered. The analysis set is identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Safety Analysis Set)

14.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first followed by ‘PIPE-505’ and an overall column (if applicable).

14.2.5. Body of the Data Display

14.2.5.1. General Conventions

Data in columns of a table or listing are formatted as follows:

14.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	n
severe	0
moderate	8
mild	3

[redacted]

- If the categories are not ordered in the CRF (e.g., Medical History, Adverse Events, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included. Medical history terms and Adverse Events terms are sorted by descending frequency of system organ class (SOC) and then by descending frequency of preferred term within each of SOC.

- Notes are added to the footnote in the TFL shell and each note starts with a new line.

- If the categories are ordered in the CRF (e.g., Discontinuation from the study etc.), then display all the categories in the same order as displayed in the CRF.

- Unknown and/or Missing categories are added to each parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

```
n                          XX
Mean (SD)                  XX.X (XX.XX)
Median                     XXX.X
Min, Max                   XX, XX
```

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, footnotes and/or programming notes will identify the selection criteria.

- Where a category with subheadings (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

14.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

[redacted]

- Units will be included where available

14.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y z’)

15. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in [redacted] SOP Developing Statistical Programs (3907).

[redacted] SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

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[redacted]

19. Shells

Tables, listings, and figure shells are provided in a separate file.

[redacted]