STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE:	Pharmaceutical Interventions for Noise-Induced Hearing Loss - Acute Exposure Treatment (PINIHL-AET)
PROTOCOL (Short Name, Version, Date):	PINIHL-WU, Version 9.0 03 March 2023
STUDY TREATMENT:	Zonisamide (ZNS)
STUDY PHASE:	Phase 2
SPONSOR:	Washington University School of Medicine
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SAP Version:	Final 6.0
SAP Version Date:	21 June 2023

Version	Date	Comments
Final 1.0	03 February 2021	Initial Version
Final 2.0	10 June 2021	• Increase in total subjects at WU and UA and sample size section updated. • Null hypothesis statements reworded. • Inclusion of stratification language at WU. • Missing data sections revised at WU and UA. • Efficacy Analysis section revised and covariates clarified at WU and UA. Sensitivity analysis added • Interim Analysis section updated. • Secondary efficacy outcome timepoint clarified at UA.
Final 3.0	21 October 2021	• Alternate hypothesis written as HA: pZNS < pplacebo

Version	Date	Comments
		• Randomization language updated to match protocols
Draft 3.1	12 January 2022	• Developed separate SAP for Washington University Study based combined WU and UA SAP v3.0.
Draft 3.2	25 February 2022	• Updated based on sponsor comments • Updated based on FDA comments
Draft 3.3	22 March 2022	• Updated based on sponsor comments
Draft 3.4	28 March 2022	• Updated to match protocol
Final 4.0	18 April 2022	• Final Version
Draft 4.1	12 January 2023	• Updated section 2.6 by removing ECG to match protocol v8.0
Final 5.0	19 January 2023	• Final Version
Draft 5.1	02 June 2023	• Updated based on FDA comments
Draft 5.2	19 June 2023	• Updated the SAS procedure for Rubin's rule in missing data analysis (Section 5.2)
Final 6.0	21 June 2023	• Final Version

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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event(s)
dB	Decibels
DPOAE	Distortion Product Otoacoustic Emissions
DSMB	Data Safety Monitoring Board
ECochG	electrocochleography
FDA	United States Food and Drug Administration
HL	Hearing Loss
hr	Hour
ITT	Intent-to-treat
kHz	Kilohertz
LAeq8hr	8 hour equivalent A-weighted sound level in decibel
mg	Milligram
NIHL	Noise Induced Hearing Loss
PGx	Pharmacogenetics
PI	Principal Investigator
PO	Per os (orally)
Post-op	Postoperative
Pre-op	Preoperative
PTS	Permanent Threshold Shift
SAE	Serious Adverse Event(s)
TTS	Temporary Threshold Shift
UA	University of Akron
WIN	Word in noise
WU	Washington University School of Medicine
ZNS	Zonisamide

1 PURPOSE

This document describes the planned statistical strategies for the analysis of data for the "Pharmaceutical Interventions for Noise-Induced Hearing Loss–Acute Exposure Treatment (PINIHL-AET)" Study. The document will be shared with the members of the Data Safety Monitoring Board (DSMB) and will be modified based on their feedback and requests.

Data reports will be prepared for the DSMB and will be part of the DSM report that will be prepared by the study team with assistance from the study statistician. The DSM report will be prepared for the DSMB semi-annually and at other times at the discretion of the DSMB. The DSM report will be reviewed by the DSMB, and will be submitted to the PI. The DSMB must meet at least every six months beginning six months after study activation at Washington University beginning six months after enrollment of the first patient at the secondary site, or due to Adverse Events (AE) or Serious Adverse Events (SAEs) to ensure subject safety through data, process or conduct of study and recommend to the sponsor on continuation, modification, or termination of the study, and no more than one month prior to the due date of the DSM report to the PI.

In the event of future amendments to the protocol, this SAP will be modified as necessary to account for changes relevant to the statistical analysis.

1.1 RESPONSIBLITIES

Pharm-Olam will perform the statistical analyses and is responsible for the production and quality control of all derived datasets and tables, listings, and figures.

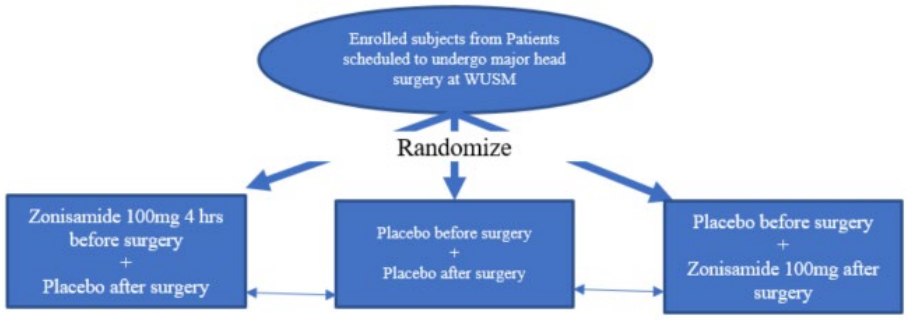
2 INTRODUCTION

2.1 STUDY DESIGN

This study is a randomized, double-blinded, placebo-controlled trial with three parallel groups, to make use of a common control group between the experimental groups. Subjects will be randomized in a balanced fashion into one of 3 arms: Zonisamide (ZNS) pre-op, Placebo, or ZNS post-op.

Study Subjects will be recruited from the Washington University Otology clinics. Patients will be offered participation if they are undergoing skull-based surgery as part of their standard treatment. These are patients that would be recommended skull-based surgery despite this investigation and this investigation will have no influence on treatment recommendations.

Figure 1 Overall Study Design



2.2 STUDY OBJECTIVES

2.2.1 Primary Objective

To determine if preoperative and/or postoperative ZNS is more effective than placebo at preventing a permanent threshold shift (PTS) in the contralateral ear of patients undergoing drilling during skull base surgery.

The primary efficacy outcome will be the proportion of PTS-positive subjects defined as the ratio of PTS-positive subjects to total number of subjects in each study arm/group. PTS positive will be defined as all subjects who in audiogram are identified as having a PTS of $\geq$ 10 dB HL increase at any frequency between 2-6 kHz post-surgery as compared to baseline audiogram.

2.2.2 Secondary Objectives

To determine if preoperative and/or postoperative ZNS is more effective than placebo at preventing a temporary threshold shift (TTS), synaptopathy, and degraded speech perception in the contralateral ear of patients undergoing drilling during skull base surgery.

2.2.3 Exploratory Analysis

To identify a genetic risk profile associated with drilling-induced hearing loss we will survey known genetic markers associated with NIHL including markers in CDH23, PCDH15, EYA4, MYO1A, KCNMA1 and OTOG1 and zonisamide (ZNS) metabolism, CYP2C9 and CYP2C192. If significant associations are observed and validated in a subsequent clinical study, we will optimize drug dosages based on a subject's genetic profile.

2.3 Study Population

We plan to enroll approximately 234 subjects over approximately 4 years. Subjects will be randomized in a balanced fashion into one of the 3 arms: ZNS 100 mg pre-op, Placebo, or ZNS 100 mg post-op. We proposed the three-group design in order to establish a common control group between the experimental groups. Enrolled study subjects will be randomized into three equal groups. The placebo group is the common group for comparison to each active group independently. Alpha error will be adjusted for multiple comparison.

2.4 Randomisation

Eligible subjects will be randomized in a balanced fashion into one of the 3 arms: ZNS 100 mg pre-op, Placebo, or ZNS 100 mg post-op. To balance noise-exposure history across study arms we will employ stratified randomization. The subjects will be stratified based on noise exposure survey responses (see table below), and will then be randomized to study groups. Randomization will be based on the randomization list generated by unblinded statistician using a computer algorithm written in SAS® using randomly selected blocks of sizes 3. Within each block of 3, there will be 1 subject assigned to each study group. The random assignment of subjects to the different study groups will be associated with consecutively assigned random numbers which will be unique for each study subject. The stratified kit list will be provided to Advanced Rx who will package and label the drug for shipment to the pharmacist. Each kit will contain two bottles and will be labeled with the same kit number. The bottle will not contain any information of the treatment allocation. One interim analysis is planned, once 33% (n=78) of the subjects have completed participation in the study.

Name	Description
1: High Noise	Screening: LENS-Q Adapted for Surgical Noise Study – 1A Or 2A Or 4A = a.Daily, Or b.Less than daily/more than weekly, Or c.Weekly, Or d.Less than weekly/more than monthly Or e.Monthly OR 1C Or 2C Or 3C >= 5 Years

Name	Description
2: Low Noise	Screening: LENS-Q Adapted for Surgical Noise Study – 1A AND 2A AND 4A = f.Less than monthly/more than yearly, g.Yearly, h.Less than yearly Or i.Never OR 1C AND 2C AND 3C < 5 Years

2.5 Treatment Assignment and Blinding

To ensure double-blinding of the trial, each subject will be randomized to one of three treatment arms via an interactive randomization tool (IRT) and assigned to a study group. Once randomized, each subject will be provided a kit on the day of surgery that contains two bottles, with one package labeled to be taken prior to surgery, and another package designated to be taken within 12 hours after surgery or when patient is released clinically to oral medication. For subjects randomized to "ZNS pre-op", the pre-op package will contain one ZNS capsule of 100 mg, and the post-op package will contain one placebo capsule that looks and tastes the same as ZNS capsules. For subjects randomized to "ZNS post-op", the pre-op package will contain one placebo capsule and the post-op package will contain one ZNS capsule of 100 mg. For the subjects randomized to "placebo", both pre- and post-op packages will contain capsules of placebo.

The study will be "masked" or "blinded" in the sense that all the study subjects and the study team members will be blinded to the assignment in the study groups. Only the pharmacist who will prepare the study drug kits and the unblinded Statistician will have access to the kit assignments. A copy of the randomization kit list with study ID assignments will be saved in a limited access folder on a secure network server at Pharm-Olam. The Medical Monitor will be contacted in emergent medical cases when knowing the treatments assignment is mandatory for clinical care of the patient.

At the time when we will need to "freeze" the data sets for purposes of developing the DSMB report, a series of SAS programs will be run from an independent programmer to produce data for each pairwise comparison into two subsets of data from the total cohort. Each subset will be de-identified. A previously prepared SAS code will be run in each subset and the output will be used to complete the table shells. Table shells will be blinded. If DSMB members find any safety issues, they may request specific unblinded data. The programmer preparing subsets will not be involved in the handling of data forms or the analysis of data. Table shells for DSMB (content and formats) will be agreed upon prior to start of study.

2.6 Schedule of Assessments and Procedures

Table below summarizes the calendar of study activities and assessments

	Screening / Baseline	**Surgery**	**Post-op**	
	Within 30 days (+3 days) prior to surgery		**Within 12 Hours**	**Within 30 days (+/- 3 days)**
Informed consent	X			
Clinical Exam	X			
Demographic Info	X			
Pre-Op Data (pregnancy test, lab results (electrolyte panel, BUN, Cr, ALT, and AST)	X			
Current Meds	X			
Questionnaire	X			X
Audiogram	X			X
ECochG	X			X
DPOAE	X		X*	X
WIN	X			X
Randomization	X			
Oral Dose**		X	X	
Blood draw***			X	
AE assessment		X	X	X

* Within 8 hours

**Dispensed on the day of surgery with instruction to take first dose prior to surgery and second dose after surgery.

*** Plasma sample for PGx will be collected at baseline visit. Plasma sample for ZNS level and PGx, electrolyte panel, BUN, Cr, ALT, and AST will be collected 12 hours after first dose.

2.7 Sample Size Determination for The Primary Efficacy Outcome Measure

The primary efficacy outcome will be the proportion of PTS positive subjects defined as the ratio of PTS-positive subjects to total number of subjects in each study arm/group. Using pilot data from a retrospective chart review of 75 similar patients undergoing ≥1-hour drill noise exposure, we estimate the proportion of PTS positive subjects in the placebo group will be 50%. We hypothesize that the expected effect of ZNS either pre-op or post-op will be a 50% reduction of the proportion of subjects with PTS positive as compared to placebo group. This is the desired clinically significant effect for treating hearing loss for single dose of 100 mg ZNS.

The sample size for this study was calculated for the planned comparisons of each of the ZNS groups with the placebo group using a balanced design and a one-sided alpha level of 0.0125 Based on the data from our retrospective study, using Fisher's exact test we estimated that 78 subjects in the ZNS group and 78 subjects in the placebo group will be needed to provide us with 80.4 % power to detect a 50% reduction in the proportion of PTS positive subjects *(from 50% to*

25% corresponding to an absolute proportion difference of 25%) at the 1-sided alpha level of 0.0125 for each ZNS-Placebo group comparison. A total of 234 subjects will be enrolled to be randomized in this study. All efforts will be made minimize and eliminate drop outs. Given the short term-follow-up of study subjects in a period where they are under medical care, few, if any, drop-outs or lost to follow-up are expected.

Sample size calculations were carried out using PROC POWER procedure in SAS 9.4.

3 Study Outcomes

3.1 Primary estimand

The primary estimand for the study is: In adults with no more than a mild to moderate high-frequency hearing loss and who undergo drilling during skull-based surgery, what is the difference in the proportion of patients experiencing PTS in the contralateral ear (the proportion of PTS-positive subjects defined as the ratio of PTS-positive subjects (defined as all subjects who in audiogram are identified as having a PTS of > 10 dB HL increase at any frequency between 2-6 kHz post-surgery as compared to baseline audiogram) to total number of subjects in each study arm/group) between ZNS treatment compared to Placebo, 30 days (+/- 3 days) after randomization or death (whichever occurs first).

3.2 Primary Efficacy Outcome

The study is designed to test the null hypothesis associated with the primary efficacy measure. The primary efficacy outcome will be the proportion of PTS-positive subjects defined as the ratio of PTS-positive subjects to total number of subjects in each study arm/group. PTS positive will be defined as all subjects who in audiogram are identified as having a permanent threshold shift (PTS) of ≥10db HL increase at any frequency between 2-6 kHz post-surgery as compared to baseline audiogram. A SAS code will be written to code all the patients for whom the difference at any frequency from 2-6 kHz in hearing thresholds (30 days (+/-3 days) post-surgery - Baseline) is ≥10 dB HL as PTS-positive. If this difference will be less than 10dB then the patients will be coded as non-PTS positive.

For the primary outcome measure, the null and alternative hypotheses for each pairwise comparison are provided below.

3.2.1 Comparison of the proportion of PTS-positive patients between ZNS pre-op and Placebo

$H_0 : p_{ZNS_{pre-op}} - p_{Placebo} = 0$ $H_A : p_{ZNS_{pre-op}} < p_{Placebo}$

We hypothesize that ZNS pre-op will reduce the proportion of PTS-positive patients by an absolute difference of 25% as compared to placebo

3.2.2 Comparison of the proportion of PTS-positive patients between ZNS post-op and Placebo

$H_0 : p_{ZNS_{post-op}} - p_{Placebo} = 0$ $H_A : p_{ZNS_{post-op}} < p_{Placebo}$

We hypothesize that ZNS post-op will reduce the proportion of PTS-positive patients by an absolute difference of 25% as compared to placebo. Our one-sided hypothesis is supported by animal studies, and lack of any evidence of hearing loss as a side effect of ZNS in human studies. The statistical testing will be performed using Bonferroni method to control for type I error rate at one-sided alpha level of 0.0125.

3.3 Secondary efficacy outcomes

The secondary outcome measures are key audiological and clinical assessments of hearing loss as listed below as continuous level variables.

- DPOAE: Distortion product otoacoustic emissions will be measured at baseline (before surgery), as well as within 8 hours and at 30 days (+/- 3 days) post-surgery to measure both temporary and permanent change in DPOAE amplitude relative to baseline. A change is noted in DPOAE amplitude at any frequency that is significantly greater than the stability of each measurement (i.e., 95% confidence interval of each measurement do not overlap).
- ECochG: Electrocochleography will be measured at baseline (before surgery) and at 30 days (+/- 3 days) post-surgery to measure change in ECochG AP amplitude, latency, and width.
- WIN testing: The Words in Noise Test will be administered at baseline (before surgery) and at 30 days (+/- 3 days) after surgery. The respective scores will be converted to Z-scores to evaluate any change in scores relative to baseline.

The study will also include an exploratory analysis aiming to identify biomarkers of response to ZNS.

3.4 Safety measures

AE and SAE that are temporally related to the intervention (beginning at time of dose through post-dose) will be evaluated for regulatory reportability as per FDA and IRB requirements. The PI and study team will review data in real time for safety. We will closely monitor and report all AE and SAE in the study per requirement.

Potential known side effects from the administration of ZNS:

- Somnolence
- Anorexia
- Dizziness
- Ataxia
- Agitation/irritability
- Difficulty with memory and/or concentration

ZNS may cause serious side effects including:

- Serious skin rash that can cause death.
- Serious allergic reactions that may affect different parts of the body.
- Less sweating and increase in body temperature (fever).
- Suicidal thoughts or actions in some people.
- Increased level of acid in blood (metabolic acidosis).
- Problems with concentration, attention, memory, thinking, speech, or language.

4 Analysis Populations

4.1 Target population

Target population includes all patients that meet the inclusion/exclusion criteria as defined in the study protocol.

4.2 Intent-to-treat (ITT) sample

ITT sample will include all subjects who are randomized. Following principles of intent-to-treat analysis all subjects will be analyzed in the treatment group they were randomized to when they were enrolled in the study.

4.3 The safety sample

The safety sample will include subjects from the full analysis population who will be enrolled and will receive active or placebo ZNS. Adherence to protocol does not affect inclusion in safety population. subjects are evaluated from the time of dose administration through two weeks post dose for drug related adverse events.

4.4 Per-protocol sample

The per-protocol sample will be limited to subjects who will be randomized and treated in compliance with the protocol. Only observations or specimens collected according to the protocol will be included in the analyses using the per-protocol population. If a subject will receive one or more treatments out of compliance with the protocol schedule, any observations or specimens collected after the out-of-compliance treatment will be excluded from the analyses using the per-protocol population.

The overall timing associated with the study is based on our previous clinical study experience. Approximately 50 patients per year receive skull surgery that requires 1 hour or more of drilling time at Washington University School of Medicine (WU). We estimate to finish the study within 4 years. If subject enrollment numbers are consistently below expectations as determined by the study team and DSMB, plans will be made to add additional sites or adjust study inclusion criteria (e.g. including head/skull surgeries requiring less than 1 hour of drilling time).

Serious feasibility or design difficulties: If one year after the start of the trial, < 50% of the planned accrual goals are met, DSMB and the study team will discuss difficulties in recruitment. Patient remuneration will be revised, if needed. If there are not enough patients meeting inclusion/exclusion criteria, then the criteria will be revised without impacting study objectives. If there are not enough patients that undergo more than 1-hr drilling time during surgery, we will explore including into the study, patients with drilling time at least 45 minutes, expanding audiometric criteria, or expanding to different institutions.

5 GENERAL ASPECTS FOR STATISTICAL ANALYSES

5.1 General Methods

- All analyses and summaries will be produced using SAS® version 9.4 (or higher).
- Standard descriptive statistics will be used to describe distribution of demographic, clinical, and audiometric characteristics as well as outcome measures for all the study samples listed in section 4. For continuous level characteristics Q-Q plots and Shapiro-Wilk test will be used to test assumption of normality. If continuous level data is found to be normally distributed data, mean and standard deviation will be used as descriptive statistics, and if the assumption of normality is violated, we will report median and range for description of these variables. Frequency and relative frequency will be used for description of categorical level variables.
- The same number of decimal places as in the raw data will be presented when reporting range, 1 more decimal place than in the raw data will be presented when reporting the mean and median, and 2 more decimal places than in the raw data will be presented when reporting the standard deviation.
- Unless stated otherwise, tabular summaries will present columns for the active treatment arm ("ZNS pre-op" and "ZNS post-op"), placebo arm, and overall.
- Unless stated otherwise, the relative frequency will be based on the number of non-missing observations. The column header will still contain the number of subjects in the treatment group. There will be a row for the number of non-missing observations in the table (at each time point, if required) for each variable being summarized.
- Any calculated p-values will be presented to 3 decimal places; p-values less than 0.001 will be presented as 'p<0.001' and p-values greater than 0.999 will be presented as 'p>0.999'.
- All relevant subjects data will be included in listings and sorted by treatment group, subject ID, and visit, as applicable, for all randomized subjects.
- Unscheduled or repeat assessments will not be included in summary tables unless specified. All assessments will be included in the subject listings.
- All tables, listings and figures will include footers that identify the name of the program that created the output, together with the date and time on which it was created. Headers will include the total number of pages that the presentation contains and, for each page, the number of the page within the presentation.

5.2 Missing Data

Every attempt will be made to ensure data completeness. We do not anticipate much loss to follow-up because of the relatively short time follow-up interval. Conservatively, we would estimate that fewer than 5% of subjects will drop out/withdraw from the study. The subject will be withdrawn from the study follow-up and procedures if the subject withdraws consent, or the sponsor decides to close the study.

Data loss, if any, would almost likely be due to subjects refusing to complete or not returning at all for the post-surgery assessment of PTS 30 days (+/- 3 days). If the subject reschedules the post-surgery appointment for a later date for any reason, and if this delay is within 30 days of the

scheduled date, the data will be considered valid and used in the efficacy analysis. Any measure outside this time window of +30 days will be defined and considered as missing data.

Missing PTS at 30 days will be imputed using SAS PROC MI procedure within each treatment group using the distribution implied by the non-missing data for the specific treatment group. The SAS code below using Multiple Imputation by Chained Equations (MICE) via the Fully Conditional Specification (FCS) statement will be used to impute the missing data under the missing at random (MAR) assumption.

```
PROC MI DATA=X SEED=<value> NIMPUTE=10  OUT=MI_OUT1 NOPRINT;
CLASS  GROUP;
VAR AGE PTA LSurg……;
FCS LOGISTIC(PTS);
RUN;
```

Each of the 10 complete data sets will be then analyzed using Fisher's exact test. One-sided p-value (p_i) from Fisher's exact test will be converted to a z-value using the inverse Normal transformation [1,2], i.e. z_i=Φ^(-1) (1-p_i), where Φ^(-1) (·) represents the inverse standard Normal cumulative distribution function.

SAS funtion to convert Fisher's exact P-value to Z-value is as follows:

```
Z_i= QUANTILE('NORMAL', p_i, 0, 1);
```

The estimated z-vales from the 10 imputed datasets will be then combined following Rubin's rules using PROC MIANALYZE procedure in SAS which will be of the form:

```
PROC MIANALYZE DATA=Y;
   MODELEFFECTS Z_i;
   STDERR Z_i;
   ODS OUTPUT ParameterEstimates=XX;
RUN;
```

The pooled estimate of z-vales from PROC MIANALYZE procedure will be then converted to probability value using the following SAS function:

```
P_value=PROBNORM(estimate);
```

6 STUDY SUBJECTS

6.1 Disposition of Subjects

Subject disposition data will be summarized by treatment group and overall for the ITT Sample Set. The number randomised, treated, completed or discontinued from the study, including reasons for discontinuation as well as the number of subjects in each sample set and subject treatment status will be summarized descriptively.

All disposition data will be listed. Inclusion and exclusion criteria will also be listed.

6.2 Demographics Characteristics

Demographic characteristics will be summarized descriptively by treatment group for the Safety Sample Set, including:

- Age (years) at time of consent
- Sex
- Ethnicity
- Race

Demographics characteristics will be listed.

6.3 Medical History and Surgical History

Medical and surgical history will be coded with Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 and summarized by System Organ Class (SOC), Preferred Term (PT), and by treatment group with counts and relative frequency based on the Safety Sample Set. A subject will only be counted once in an SOC and an SOC/PT combination.

All medical history data will be listed.

6.4 Concomitant Medications

Concomitant medications are defined as all medications (excluding study dose) taken on or after the date of first dose administration up to and including the date of the post operative Day 30 visit.

Medications that started before the date of first dose and are ongoing after the date of first dose will be considered as concomitant medications.

Medications will be coded using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug name according to the World Health Organization (WHO) Drug Global B3, (March 2021). Summary table will be provided for concomitant medications for the Safety Sample Set, presenting the number and relative frequency of subjects by treatment group, and will be sorted in alphabetical order of ATC Level 2 and then PT in the overall column. For each subject, the medication will be counted only once within a given ATC level 2 and only once within a given preferred drug name level. A subject may appear more than once if she has more than one concomitant medication coded under different ATC categories.

Concomitant medications will be presented in a listing..

6.5 Treatment Administration

The number of doses taken will be summarized by treatment group and overall for the Safety Sample Set and include

- Number and percentage of subjects who received dose 1
- Number and percentage of subjects who received dose 2
- Number and percentage of subjects who received both doses

Dose administration information will be listed for all safety subjects.

6.6 Protocol Deviations

Protocol deviations will be summarized for the Safety Sample Set by type of deviation. Protocol deviations for all subjects who signed an informed consent will be entered into Pharm-Olam's Clinical Trial Management System. Examples of deviation types may include but are not limited to:

- Inclusion/exclusion criteria not met
- Informed consent
- Randomization
- Essential/Study Documents
- Investigational product administration and handling
- CRF/source data
- Sample/tests handling
- Equipment/Facilities
- Visit procedures
- Other

Protocol deviations will be reviewed by Washington University and Pharm-Olam medical and clinical (including statistical) personnel and classified as major or minor deviations at a blinded data review meeting prior to database lock.

Major protocol deviations are defined as those that may significantly impact the quality (i.e., completeness, accuracy, and reliability) or integrity of key trial data; or indicates systemic problem within the study or its conduct; or that might significantly impact the rights, safety or welfare or trial subjects.

Protocol deviations will be presented in each deviation category as a major or minor deviation by treatment group. The total count of protocol deviations within each treatment group will be used as the denominator for relative frequency in this table. All protocol deviations will be presented in a data listing.

7 EFFICACY ANALYSES

All efficacy analyses will be carried out using the Intent-to-treat Sample and Per-Protocol Sample.

7.1.1 Analysis of primary outcome variable

Efficacy analysis at the end of the study

The primary outcome measure for assessing effectiveness of ZNS (100 mg PO) either pre-op or post-op compared to the placebo group will be the proportion of subjects defined as PTS positive 30 days (+/-3 days) after surgery.

Audiogram will be performed to look for PTS. Patients for whom the difference at any frequency from 2-6 kHz in hearing thresholds (30 days (+/-3 days) post-surgery - Baseline) is ≥10 dB HL will be defined as PTS positive. Primary analysis and sensitivity analyses will be carried out on the primary endpoint.

Primary analysis

Frequency and relative frequency will be used to describe the distribution of the primary outcome measure in each study group. To assess efficacy, Fisher's exact test will be used to compare the proportion of subjects with PTS positive in ZNS group with the proportion of patients with PTS positive in the placebo group.

The confidence intervals will be calculated using method 10 described by Newcombe RG, 1998 and also described by Altman et al.

1. Altman, Douglas, et al., eds. Statistics with confidence: confidence intervals and statistical guidelines. https://www.amazon.com/Statistics-Confidence-Intervals-Statistical-Guidelines/dp/0727913751

Let n_1 be the number of participants in placebo group, and r_1 the number of participants with PTS in the placebo group. $p_1=r_1/n_1$ be the proportion of PTS in the placebo group, and q_1=r2/n2the proportion of participants that do not have PTS in placebo group.

l_1 and u_1 are the lower and upper limits of the 100(1-α)% confidence interval for p_1

Using Wilson method we calculate:

$$A_1 = 2r_1 + z^2$$

$$B_1 = z\sqrt{z^2 + 4r_1 q_1}$$

$$C_1 = 2(n_1 + z^2)$$

$$l_1 = \frac{(A_1 - B_1)}{C_1} \qquad u_1 = \frac{(A_1 + B_1)}{C_1}$$

z_a = the $100(1-\alpha)^{th}$ percentile of the standard Normal distribution.
Let n_2 be the number of participants in ZNS group, and r_2 the number of participants with PTS in the ZNS group. $p_2=r_2/n_2$ be the proportion of PTS in the ZNS group, and q_2 the proportion of participants that do not have PTS in ZNS group.

l_2 and u_2 are the lower and upper limits of the 100(1-α)% confidence interval for p_2

$$A_2 = 2r_2 + z^2$$
$$B_2 = z\sqrt{z^2 + 4r_2q_2}$$
$$C_2 = 2(n_2 + z^2)$$

$$l_2 = \frac{(A_2 - B_2)}{C_2} \qquad u_2 = \frac{(A_2 + B_2)}{C_2}$$

z_a = the $100(1-\alpha)^{th}$ percentile of the standard Normal distribution.

The proportion difference between groups is: $D = p_1 - p_2$

The lower (l_D) and the upper limits (u_D)of 100 (1-α)% confidence interval for D will be calculated as:

$$l_D = D - \sqrt{(p_1 - l_1)^2 + (u_2 - p_2)^2}$$
$$u_D = D + \sqrt{(p_2 - l_2)^2 + (u_1 - p_1)^2}$$

A supportive logistic regression analysis will be done with covariates: age, pre-op hearing dichotomized to normal to minimal hearing loss and slight to mild loss, noise exposure history dichotomized to high risk and low risk, exposure categorized as low (8-hour equivalent A-weighted sound level in decibel (LAeq8hr) < 80 dBA), moderate (LAeq8hr > 80 dBA but < 90 dBA), or high (LAeq8hr > 90 dBA).

```
PROC LOGISTIC DATA=X;
CLASS  GROUP;
  MODEL PTS = COVARIATE1 COVARIATE2.. ;/*Covariates are as mentioned above*/
RUN;
```

Sensitivity analysis of the primary endpoint

The potential impact of missing primary endpoint data will be explored in sensitivity analyses using multiple imputation. Two sensitivity analyses performed:

Sensitivity 1: MI analysis under the missing not at random assumption (MNAR)
Sensitivity 2: Logistic regression tipping point analysis under the assumption of data missing at random.

Sensitivity 1

Proc MI procedure in SAS will be used to impute missing data for study treatment groups using the distribution implied by the non-missing patient data within the placebo group. The SAS code to impute data for Sensitivity analysis 1 under the MNAR assumption will be of the form:

```
PROC MI DATA=X SEED=<value> NIMPUTE=10  OUT=MI_OUT1 NOPRINT;
CLASS  GROUP;
VAR AGE PTA LSurg……;
FCS LOGISTIC(PTS);
RUN;
```

Post imputation each of the imputed 10 datasets will be analyzed using the same approach as for the primary outcome measure. The estimates of the analysis of the 10 imputed datasets will be then combined following Rubin's rules using PROC MIANALYZE procedure in SAS which will be of the form:

```
PROC MIANALYZE PARMS=GMPARMS COVB=GMCOVB PARMINFO=GMPINFO WCOV BCOV
    TCOV; / *dataset "gmparms" contains the estimates and associated standard errors
for the mean parameters from each of the M=10 imputed data sets.
dataset "gmcovb" contains the asymptotic covariance matrics
dataset "gmpinfo" contains parameter info*/

    MODELEFFECTS INTERCEPT AGE PTA LSurg……;
RUN;
```

Sensitivity 2

Multiple imputation will be used to impute data in each of the study groups. A progressive penalty of $\delta_i = k_i \times \log(OR)$ will be added to imputed values in ZNS arm where (i) OR is the Odds ratio estimate for ZNS as compared to Placebo from the primary logistic regression analysis and (ii) $k_i = 1, 0.95, 0.90, \ldots 0.05, 0$, 1.05, 1.10,… thus k ranges from 1 (equivalent to MI approach based on MAR) to 0 (or higher), until the conclusion of the primary analysis is overturned (i.e., p<0.05 is lost at, this value of k_i being the 'tipping point'). Rubin's method will be used to combine the primary endpoint treatment effects across imputations for each value, k_i, of the penalty. Forest plots will be used to graphically display the penalty value that results in loss of statistical significance.

SAS code sample for Sensitivity analysis is provided below:

```
**Step 1: Generate 10  datasets by imputing the missing data**;

PROC MI DATA=X SEED=<value> NIMPUTE=10  OUT=MI_OUT1 NOPRINT;
CLASS  GROUP;
VAR AGE PTA LSurg……;
FCS LOGISTIC(PTS);
RUN;

**Step 2: Generate 10 complete datasets from the 10 monotonized datasetsin Step 1 for
missing values in the drug arm,
```

```
subtract DELTA derived above from their imputed data.**;
proc mi data=YYY NIMPUTE=1 SEED=<value> OUT=YYY_shift;
by group;
class group;
var AGE PTA LSurg……;
monotone method=logistic;
mnar adjust(PTS / shift=DELTA adjustobs=(group='1'));
run;

**Step 3: Apply the primary MMRM to the 10 complete datasets in Step 2**;
proc genmod data=YYY_shift descending;
by _imputation_;
class group;
model PTS = group AGE PTA LSurg……;
ods output GEEModPEst=gmparms;
run;


**Step 4: Obtain the pooled inference from 10 sets of estimates from Step 3**;

PROC MIANALYZE PARMS=GMPARMS COVB=GMCOVB PARMINFO=GMPINFO WCOV BCOV
    TCOV;
    MODELEFFECTS group;
RUN;
```

7.1.2 Analysis for secondary outcome measures.

The focus of the study is to determine efficacy of ZNS for treatment of acute hearing loss based on the testing of hypothesis for primary outcome. In addition, we will also conduct analysis to evaluate other important audiologic measures. The secondary outcome measures are key audiological and clinical assessments of change in cochlear function and hearing loss: DPOAEs, ECochG, WIN testing. They will be measured as continuous level variables. We do not plan any adjustment of alpha error for multiple comparisons.

Analysis of variance (ANCOVA) will be used for comparison of outcome measures between each of the ZNS groups and placebo study group after controlling for baseline value and age, pre-op hearing dichotomized to normal to minimal hearing loss and slight to mild loss, noise exposure history dichotomized to high risk and low risk, exposure categorized as low (LAeq8hr < 80 dBA), moderate (LAeq8hr > 80 dBA but < 90 dBA), or high (LAeq8hr > 90 dBA).

7.1.3 Pharmacogenetics analysis plan

This analysis will be performed at the end of the trial by Gateway Biotechnology. To identify genetic variants associated with ZNS protection against hearing loss, we will utilize genetic and metabolic data collected from patients in a genetic association study. Variables including sex, age, normalized values (Z-scores) of drug plasma concentration, Z-scores of noise intensity and duration, and Z-scores of hearing functions measured immediately following surgery will be included in the analysis of variance. Single-marker allelic association analyses will be conducted on the two imputed data sets using PLINK v1.07. The data will be analyzed with a logistic regression model on the additive continuous dosage of minor alleles from 0 to 2 to account for uncertainty of imputation. We will combine association results in the two cohorts by performing

a genome-wide inverse-variance weighting meta-analysis using PLINK v1.07, and assuming a fixed-effect model. Functional annotation of top-associated markers will be performed with R package NCBI2R 1.4.6 (http://CRAN.Rproject. org/package=NCBI2R), and key regional association plots of meta-analyzed results will be generated. To confirm whether these variants are specific to ZNS response, we will apply CEP SKAT to analyze genetic associations based on Z-scores of audiogram average threshold shifts and DPOAE amplitudes. All genetic variants, including both common and rare variants, will be included in this association study. Age, gender, drug concentration, and noise duration and intensity will be adjusted for the analysis. The analysis will also be performed using hearing data collected two weeks following surgery. The only differences will be a) using the Z scores of ECochG AP amplitude, latency, and width as well as WIN score, and b) using average audiogram threshold shifts and DPOAE amplitudes at 30 days (+/- 3 days) post-treatment. We will also include metabolite profiling data to support potential genotypic responses to drug treatments. To control for confounding effects, these models will be adjusted for age, gender, and noise duration and intensity. Finally, the control and ZNS-treated comparisons will be performed using post-hoc comparisons with a Bonferroni adjustment for multiple comparison testing. Statistical analyses will be performed using the CEP-SKAT method in R language, and the statistical software SAS version 9.4 for Windows will be used for additional analysis.

8 SAFETY ANALYSES

All safety analyses will be carried out using the Safety Sample Set.

Descriptive statistics will be used to summarize all AEs and SAEs. Frequency and relative frequency will be used to present the number of subjects with AEs, SAEs, and with each specific event. We will explore the expected and unexpected adverse events.

8.1.1 Safety monitoring

Adverse events will be tracked for the WU site from the time of dose administration through two weeks post dose for drug related adverse events Laboratory testing (electrolyte panel, BUN, Cr, ALT, and AST) done as part of the study conducted at WU site, will be collected post dose within 12 hours. In the event the lab values are not within normal limits post dose, the PI will be notified and recommend that the subjects be evaluated by his/her treating physician. Study subjects will remain in the study and lab tests repeated until within normal limits. All adverse events will be documented and assessed for relatedness to the study medication.

The study team will monitor for adverse events on an ongoing basis. Once the team becomes aware of an adverse event, the AE will be reported according to institutional guidelines. Reporting requirements for Washington University study team may be found in Section 1.1 of protocol. Reporting requirements for secondary site study teams participating in Washington University-coordinated research may be found in Section 1.2 of protocol.

Early stopping rule related to serious adverse events: In the event of a serious adverse event, DSMB will evaluate the association of the serious adverse events with the study arm, break the blind if needed, and if found to be associated with treatment, DSMB will consider the study for revision or stopping.

8.2 Clinical Laboratory Tests

Biochemistry blood tests will be performed at screening for all subjects.

The following biochemistry laboratory parameters will be measured: Chloride, sodium, potassium, Carbon dioxide, Blood urea Nitrogen (BUN), creatinine, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST).
Laboratory test results will be summarized descriptively by treatment group using Safety Analysis Sample.

All clinical laboratory results will be listed. Laboratory values that are outside the normal range will be flagged.

8.3 Clinical Examination of the Ears

A clinical examination of ears will be performed at screening. Overall results will be recorded as Normal, Abnormal Not Clinically Significant, or Abnormal Clinically Significant.

The frequency and relative frequency of the overall assessment of the clinical examination will be summarized for screening visit by treatment group.

Clinical examination results will be listed.

8.4 Electrocardiogram (ECG)

A ECG was to be performed at screening for all subjects prior to protocol version 7.0, and no longer performed with changes in protocol 7.0. EGC parameters include heart rate, PR Interval, RR Interval, QRS Duration, QT Interval, and QTcF. Actual values of each ECG parameter at the screening visit will be summarized using descriptive statistics if requested upon final analysis.

All ECG results will be listed if requested upon final analysis.

8.5 Pregnancy Test

A pregnancy test (serum/urine) will be performed in female subjects of childbearing potential at screening. Pregnancy test results will be listed.

9 INTERIM ANALYSIS

A sponsor blinded interim analysis focused on the primary endpoint after 33% of the patients have completed participation in the study (26 in each group). The independent programmer will prepare the datasets for each pairwise comparison (subsets of data) using a pre-prepared SAS code and will freeze them for the interim analysis. To ensure the double blinding of the study the subjects will not be presented in the assigned groups. The blinded statistician will estimate the overall proportion of PTS positive subjects in each group. Then one-sided Fisher's exact test will be used to compare the proportion of subjects with PTS positive in ZNS group with the proportion of patients with PTS positive in the placebo group. one-sided p-value (p_i) from Fisher's Exact Test will be converted to a z-value using the inverse Normal transformation [1,2], i.e. $z_i = \Phi^{-1}(1 - p_i)$, where $\Phi^{-1}(\cdot)$ represents the inverse standard Normal cumulative distribution function.

For each pair-wise comparison, with 33% information, the trial would be stopped for futility if the interim z-value <= 0.6850 for either or both comparisons, corresponding to a conditional power of ≤10% for each comparison. This design would provide 79.6% overall power (i.e. the probability of passing futility and reaching p<0.0125 for one or both comparisons in the final analysis would be 79.6%).

Based on interim analysis the following actions may be taken:

- Stop only one of the ZNS groups for futility
- Stop the trial (both ZNS groups) for futility
- Continue the trial as planned.

10 SOFTWARE AND PROGRAMMING SPECIFICATIONS

All datasets, TLFs, and statistical analyses will be generated using SAS, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). Computer-generated datasets, table, listing and figure output will adhere to the following specifications:

10.1 General Programming Specifications

- One SAS program can create several outputs or a separate SAS program can be created for each output at statistical programmer's discretion.
- Each output will be stored in a separate file.
- Dataset files will be delivered in SAS7BDAT format.
- TLF output files will be delivered in Word format / rtf format (or in pdf format if sponsor requests).

10.1.1 General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8, in sentence case.
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8, in sentence case.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. 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.

10.1.2 Headers

- All output should have the following header at the top left of each page:

  Washington University School of Medicine
  Protocol: PINIHL-WU
  Data Cutoff Date: ddMonyyyy

- All output should have Page n of N at the top or bottom right corner of each page. TLFs should be 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).
- The date (date output was generated) should appear along with program name and location as the last footer on each page.

10.1.3 Display Titles

Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The sample set should be 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)
Sample Set

10.1.4 Column Headers

- Column headings should be 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.
- Sample 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 sample set.

10.1.5 Body of the Data Display

10.1.5.1 General Conventions

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

- alphanumeric values are left-justified;
- whole numbers (e.g., counts) are right-justified; and
- numbers containing fractional portions are decimal aligned.

10.1.5.2 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 should be 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

Where relative frequencies are presented in these tables, zero relative frequencies will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any 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 should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum (range) should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Range	XXX - XXX

- P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. If the p-value should be less than 0.0001 then present as <0.0001. If the p-value is returned as >0.999 then present as >0.999
- Relative frequency values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Values that round down to 0.0 will be displayed as ‘<0.1’. Unless otherwise noted, for all relative frequencies, the number of subjects in the sample set for the treatment group who have an observation will be the denominator. Relative frequency after zero counts should not be displayed and Relative frequency percentages equating to 100% should be presented as 100%.
- Unless otherwise specified, tabular displays of data for medical history, concomitant medications, and all tabular displays of adverse event data should be presented by the body system, drug class, or SOC by decreasing frequency, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC code), and adverse events (by preferred term) should be displayed in order of decreasing frequency. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as “-”.
- The relative frequency of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the sample set presented. However, careful consideration is required in many instances due to the complicated nature

of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and relative frequency of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (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.

10.1.5.3 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 should be 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 should be printed in SAS® DATE9.format ("DDMMMYYYY": 01JUL2000). Missing portions of dates should be 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 must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26 or 11:26:45). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

10.1.6 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.
- Footnotes will be present on the page where they are first referenced and thereafter on each page of the table, unless the footnote is specific only to certain pages. subject specific footnotes should be avoided.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display

footnotes, and only those essential to comprehension of the data will be repeated on each page.

- The last 2 lines of the footnote section will be a standard source that indicates the name of the program used to produce the data display, date and time the program was run, and the listing source (or data source for a listing) (i.e., ‘Program: myprogram.sas Listing source: 16.x.y.z’).

11 QUALITY CONTROL

11.1 Specifications

Once the SAP is finalized, dataset and TLF specifications will be developed and reviewed by the study team. An internal round table review of draft specifications will be conducted by the Lead Programmer, Lead Validator, Lead Statistician and Senior Reviewer (or member of Statistics Management).

The client will have the opportunity to review, comment and approve (via signature) all dataset and TLF specifications.

11.2 Outputs

Validation of analysis datasets and tables are conducted through independent parallel programming of the statistical output according to the agreed upon specifications defined in the protocol, SAP, table shells, and dataset specifications. In this process, two programmers working independently (i.e., without input from one another), program the same output and compare results (via SAS PROC COMPARE). Any discrepancies are discussed and resolved, and the validation cycle is repeated until no further differences are noted between the two outputs.

All programs are submitted in batch mode to document the results of the PROC COMPARE indicating no unequal observations. Additionally, tracking logs are maintained which document all QC and validation findings and their resolution.

For CDISC datasets the Pinnacle 21 report will be used to validate the datasets for CDISC compliance.

Once the validation cycle is complete, the output (dataset or TLF) is provided for the lead statistician’s review as well as an internal round table review including the Lead Programmer, Lead Validator, Lead Statistician and Senior Reviewer (or member of Statistics Management).

For the delivery of the outputs for the Blinded Data Review Meeting (BDRM) the following team members from Pharm-Olam may join the output review round table as well: Medical Writer (if applicable), Data Manager (if applicable), Medical Monitor (if applicable) and Project Manager (if applicable).

The client will have the opportunity to review, comment and approve (via signature) all final datasets and TLFs as well.

12 APPENDICES

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Figure 14.1.1	QQ Plot for Age	Safety Sample Set
Figure 14.1.2	QQ Plot for Biochemistry Lab Parameters	Safety Sample Set
Figure 14.2.1	QQ Plot for Distortion Product Otoacoustic Emissions (DPOAE) OAE Amplitude	ITT Sample Set
Figure 14.2.2	QQ Plot for Distortion Product Otoacoustic Emissions (DPOAE) Noise Floor Amplitude	ITT Sample Set
Figure 14.2.3	QQ Plot for Electrocochleography (ECochG)Parameters	ITT Sample Set
Figure 14.2.4	QQ Plot for Word in Noise (WIN) Test Parameters	ITT Sample Set