STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE:	Pharmaceutical Interventions for Noise-Induced Hearing Loss-Acute Exposure Treatment (PINIHL-AET)
PROTOCOL (Short Name, Version, Date):	PINIHL-UA, Version 7.0 23 March 2022
STUDY TREATMENT:	Zonisamide (ZNS)
STUDY PHASE:	Phase 2
SPONSOR:	Washington University School of Medicine/The University of Akron School of Speech Language Pathology and Audiology
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SAP Version:	Final 1.0
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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 University of Akron 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
Final 1.0	18 April 2022	• Final Version

Signature Page

I confirm that I have reviewed this document and agree with the content.

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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.

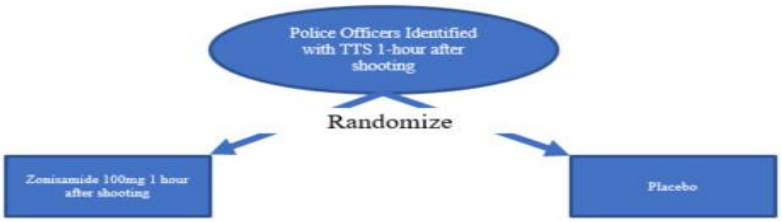
2 INTRODUCTION

2.1 STUDY DESIGN

A randomized, double-blind, placebo-controlled clinical trial has been designed. Police officers identified with TTS will be randomized to receive either ZNS or a placebo.

Study subjects will be recruited from the Akron Police Department, Summit County Police Department, and other local surrounding police departments. Police officers will be offered participation if they are training for firearm certification as part of their standard occupational requirements. These are officers that would be recommended and/or required to complete these trainings/certifications despite this investigation and this investigation will have no influence on audiologic recommendations.

Interested police officers will then undergo screening for TTS following shooting range noise exposure. Those officers identified with TTS will be randomized via an interactive randomization tool (IRT) and assigned to a study group. Once assigned the subject will be provided a kit that will contain either ZNS (100 mg PO) or a placebo.



2.2 STUDY OBJECTIVES

2.2.1 Primary Objective

To determine if ZNS is more effective than placebo in preventing permanent threshold shift (PTS) in police officers identified with temporary threshold shift (TTS) following shooting range noise exposure.

2.2.2 Secondary Objectives

To determine if ZNS is more effective than placebo in the prevention of additional auditory dysfunction in police officers following shooting range noise exposure as measured by ultra-high frequency audiometry, distortion product otoacoustic emissions (DPOAE), electrocochleography (EcochG) and words-in-noise (WIN) scores, and to determine a PGx link between NIHL and ZNS treatment effect.

2.3 Study Population

This study is a randomized, controlled clinical trial with two parallel groups. Police officers identified with TTS following shooting range noise exposure will be randomized to receive either ZNS (100 mg PO) or a placebo. We plan to enroll approximately 132 subjects (police officers) with TTS over 4 years. Subjects will be randomized in a balanced fashion into one of the two arms: ZNS (100 mg PO) or Placebo.

2.4 Randomisation

Eligible subjects will be randomized via an interactive randomization tool (IRT) in a balanced fashion into the 2 study groups based on the randomization list generated from the study statistician using a computer algorithm written in SAS® using randomly selected blocks of sizes 2. Within each block of 2, there will be 1 subject assigned to each study group. To balance noise-exposure history across study arms we will employ stratified randomization. The subjects will be stratified based on noise exposure survey responses as described in table below, and will then be randomized to study groups. The random assignment of subjects to the different study groups will be associated with consecutively assigned study identification numbers (Study ID) which will be unique for each study participant. The stratified randomization kit list will be provided to Advanced Rx who will package and label the drug for shipment to the pharmacist for each participant. Each bottle will be labeled with the kit number, study ID, and instructions on how to take the study medication. The bottle will not contain any information of the treatment allocation.

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

2.5 Treatment Assignment and Blinding

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. The Medical Monitor will be contacted. A copy of the randomization 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 study subject.

The data will be presented without having the treatment assignments of individual study subjects made known to study team members including the study PI. Table shells will be blinded. If DSMB members find any safety issues, they may request specific unblinded data. Table shells for DSMB (content and formats) will be agreed upon prior to start of study.

Subjects will receive one time dose of oral ZNS or matching placebo after training if TTS is identified on audiogram 5-30 minutes after shooting. Subjects will be instructed to take study drug without food. We will recommend that capsules be swallowed whole per the current approved labeling.

2.6 Schedule of Assessments and Procedures

The table below summarizes the calendar of study activities and assessments

	VISIT 1 Screening Assessment	**VISIT 2 Baseline Assessment**	**Post-training**		
			VISIT 3 Within 5-30 Minutes	**VISIT 4 Within 24 Hours**	**VISIT 5 30 days (+/- 3 days)*** **
Informed Consent	X				
Demographic Info	X				
Current Meds	X				
Questionnaires	X				X
Cognitive Assessment		X		X	
Clinical ear exam	X	X	X		X
Audiogram	X	X	X		X
ECochG		X			X
DPOAE		X	X		X
WIN		X			X
Sound Measurements	X	X	X		X
Randomization			X*		

	VISIT 1 Screening Assessment	**VISIT 2 Baseline Assessment**	**Post-training**		
			VISIT 3 Within 5-30 Minutes	**VISIT 4 Within 24 Hours**	**VISIT 5 30 days (+/- 3 days)*** **
Oral Dose* ZNS or Placebo			X*		
Blood draw**		X		X	
AE Assessment			X	X	X

* Dispensed after training if TTS is identified on audiogram 5-30 minutes after shooting.
** Blood draw: Electrolyte panel, BUN, Cr, ALT, and AST; DNA analysis and serum pregnancy test at baseline
***If TTS is seen from pure tones after each training session

2.7 Sample Size Determination for The Primary Efficacy Outcome Measure

Calculation of sample size for this study is based on a balanced design and a one-sided significance level of 0.025. We estimate that among officers identified as being at high risk for permanent hearing loss due to having TTS, the proportion of PTS positive officers 30 days (+/- 3 days) after shooting will be 50%. This is the proportion of PTS positive officers we expect to observe in the placebo group. Thus, for the primary outcome, we estimated that 66 officers per group will provide us with 80.5% power to detect a 50% reduction in the proportion of PTS positive officers (from 50% to 25%) at the 1-sided alpha level of 0.025 A planned total of 132 subjects is to be enrolled and randomized.

We will make all the needed efforts to eliminate drop outs, and due to short term-follow-up of the study subjects in a period we do not expect any drop-outs or lost to follow-up.

All 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 police officers who are training for firearm certification as part of their standard occupational requirements and suffer temporary threshold shift (TTS) following shooting range noise exposure, what is the difference in the proportion of officers experiencing PTS (defined as all officers who in audiogram are identified as having a permanent threshold shift (PTS) of ≥10 dB HL increase at any frequency from 2-6 kHz in at least one ear (30 days (+/- 3 days) post shooting - Baseline) to total number of subjects in each study arm/group) between ZNS treatment compared to Placebo, 30±3 days after randomization.

3.2 Primary Efficacy Outcome

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 ≥10 dB HL increase at any frequency from 2-6 kHz after shooting as compared to baseline audiogram. A SAS code will be written to code as PTS positive all the officers for whom the difference at any frequency from 2-6 kHz in hearing thresholds (30 days (+/- 3 days) post shooting - Baseline) will be ≥10 dB HL in at least one of the ears. If this difference is less than 10 dB then the officers will be coded as non-PTS positive.

To date, there are no reports of ZNS being associated with hearing damage or loss, so the hypothesis for this study will be a one-sided hypothesis.

For the primary outcome measure, the null and alternative hypotheses are provided below.

Comparison of the proportion of PTS-positive subjects between ZNS group and Placebo

$H_0: \; p_{ZNS} - p_{Placebo} = 0$ $\qquad$ $H_A: p_{ZNS} < p_{Placebo}$

We hypothesize that ZNS will reduce the proportion of PTS-positive officers 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.

Hypothesis testing for the primary outcome will be performed at the one-sided alpha level of 0.025.

3.3 Secondary efficacy outcomes

The study is designed to test the null hypothesis associated with the primary efficacy measure. Nevertheless, it provides a great opportunity to evaluate the impact of ZNS on other audiometric and clinical measures:

- DPOAEs: Distortion product otoacoustic emissions will be measured at baseline

(before shooting), as well as within 5-10 minutes after shooting and 30 days (+/-3 days) post-shooting (for officers with positive TTS) to measure both temporary and permanent changes 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).

- Ultra-high frequency audiometry: Ultra-high frequency audiometry (10-14 kHz) will be measured at baseline (before shooting), 30 days (+/-3 days) after shooting (for officers with positive TTS) to measure for both temporary and permanent high frequency audiometric changes. A significant change is defined for any frequency that is greater than 5 dB HL from baseline thresholds.
- ECochG: Electrocochleography will be measured at baseline (before shooting) and 30 days (+/-3 days) after shooting (for officers with positive TTS) to measure for changes in ECochG AP amplitude, latency and width.
- WIN testing: The Words-In-Noise test will be administered at baseline (before shooting) and 30 days (+/-3 days) after shooting (for officers with positive TTS). The respective scores will be converted to Z-scores to evaluate for any change in scores relative to baseline.

3.4 Exploratory analysis

Exploratory DNA analysis and phenotypic correlations with ZNS treatment.

3.5 Safety measures

We will closely monitor and report all the AE and SAE in the study according to Institutional guidelines.

Potential 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.

In this study we will assess cognitive performance. Cognitive assessments will be administered within 24 hours following drug intake, testing will take ≤ 20 minutes.

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 included subjects from the full analysis population who were enrolled and received active or placebo ZNS. Adherence to protocol does not affect inclusion in safety population.

4.4 Per-protocol sample

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

For this study, we have approximately 800 officers from Akron and Summit County, not including additional local police departments from which to screen and recruit, understanding a large percentage of the population may already present with significant NIHL, thus, may not meet the eligibility criteria. In a previous study by the investigators, 62-85% of police officers presented with evidence of NIHL, therefore, we need a significantly larger sample size to recruit subjects that meet our eligibility criteria. We estimate that each year we will have at least 60 officers screened within 1 hour of shooting each year. If the rate of TTS after 1 hour of shooting is that of the study from Blioskas et al, we estimate that 48 officers will qualify to undergo randomization each year. If 70% of them consent to be randomized there will be 34 officers enrolled and completing the trial each year. Based on these estimates, we will be able to meet our accrual goals and complete the study with a sample size of 132 officers in approximately 4.5 years.

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 2.5. 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 (100 mg PO)"), 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, Participant 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 participant 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 participant will be withdrawn from the study follow-up and procedures if the participant 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-shooting assessment of PTS 30 days (+/- 3 days). If the subject reschedules the post-shooting 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 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;
```

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 group;
RUN;
```

6 STUDY SUBJECTS

6.1 Disposition of Subjects

Participant 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 participant 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

Medical 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 participant 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 traing Day 30 visit (Visit 5).

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 participant, the medication will be counted only once within a given ATC level 2 and only once within a given preferred drug name level. A participant 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 the dose

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 University of Akronand 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) post-shooting compared to the placebo group will be the proportion of officers with TTS defined as PTS positive 30 days (+/- 3 days) after shooting range exposure.

Audiogram will be performed to look for PTS. Officers for whom the difference at any frequency from 2-6 kHz in hearing thresholds (30 days (+/- 3 days) post-shooting - 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 officers with PTS positive in ZNS group with the proportion of officers with PTS positive in the placebo group.
The confidence intervals will be calculated using method 10 described by Newcombe RG, 1998and 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 the 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

$$A_2 = 2r_2 + z^2$$

$$B_2 = z\sqrt{z^2 + 4r_2q_2}$$

$$C_2 = 2(n_2 + z^2)$$

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

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:

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

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

To provide an estimate of treatment effect a supportive logistic regression analysis will be done with covariates: age, pre-existing hearing loss dichotomized to normal to minimal hearing loss and slight to mild loss, noise exposure history dichotomized to high risk and low risk, average post-shooting.

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 officer 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 the hypothesis for the 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 hearing loss, and include: Audiometric TTS, DPOAEs, Ultra-high frequency audiometry, ECochG, and WIN testing 30 days (+/- 3 days) after shooting, and are 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, 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, average post-shooting TTS.
Statistical analyses will be conducted using the SAS software (SAS Institute Inc., Cary, N.C.,.

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 data collected from saliva samples to conduct 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 range shooting will be used in the analysis. Single-marker allelic association analyses will be conducted 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 to four weeks after range shooting. 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. 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 AE, 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 UA site at the follow up 14-30 day visit. All adverse events must be recorded on the AE tracking case report form (CRF). AEs related to study medication only will be tracked.

Each officer will be asked about potential study-related side effects for safety monitoring, i.e. they will be asked *"if they had any unpleasant experience, including an illness or other physical event, in the past 4 hours, whether they think it is study related or not?"* This will be followed by a question regarding their feeling of safety on the job, i.e. they will be asked *"if they feel safe partaking in required responsibilities associated with their job at this time or not?"*

Number and percentage of officers self-reporting potential study-related side effects or that report that they do not *feel safe partaking in required responsibilities associated with their job* will be reported to DSMB.

Cognitive assessments will be performed at baseline and within 24 hours following drug intake will be used to assess any side effects of ZNS on cognition. The assessments will be:

a. Digit-symbol substitution test: Measures processing speed
b. List learning task/RBANS: Measures memory function.
c. Verbal fluency test (word finding task): Measures working memory, speech/language
d. Stroop test: Measures executive functioning (vigilance, attention, inhibition).

Paired samples t-test will be used to explore the change from baseline to 24 hours following drug intake for each of the cognitive assessment instruments. The within subject change will be also compared to clinically meaningful differences for each of the test, to assess whether the observed change is clinically/practically important. Results of this analysis will be presented to DSMB.

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 University of Akron study team may be found in Section 1.1 of protocol. Reporting requirements for secondary site study teams participating in University of Akron-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 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 officers have completed participation in the study (22 in each group). The independent programmer will prepare the dataset 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. Then 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.

With 33% information, the trial would be stopped for futility if the interim z-value <= 0.5233 corresponding to a conditional power less than 10%. This design would provide 79.4% overall power (i.e. the probability of passing futility and reaching p<0.025 for the comparison in the final analysis would be 79.4%).

Based on interim analysis the following actions may be taken:

- Stop the trial 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:

  University of Akron
  Protocol: PINIHL-UA-1
  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 participant 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 participant can be included in more than one category, describe in a footnote or programming note if the participant 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, participant number, visit/collection day, and visit/collection time.
- Missing data should be represented on participant 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 participant listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the participant 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. Participant 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.

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