STATISTICAL ANALYSIS PLAN

A PROSPECTIVE, MULTICENTER STUDY TO EVALUATE EFFECTIVENESS AND SAFETY OF LIDOCAINE IONTOPHORESIS AND TYMPANOSTOMY TUBE PLACEMENT USING THE TULA IONTOPHORESIS AND TUBE DELIVERY SYSTEMS FOR ADULTS IN AN OFFICE SETTING (ADEPT; ADult study to Evaluate Placement of tympanostomy Tubes in-office)

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1.0 Scope

This is the Statistical Analysis Plan (SAP) for the final analysis of data collected under Protocol Number CPR007003.

2.0 Trial Objectives

The objectives of the study are two-fold:

1) to determine if active lidocaine iontophoresis is superior to sham lidocaine iontophoresis in providing anesthesia to the tympanic membrane, and

2) to evaluate tolerability and safety of tympanostomy tube (TT) placement in adults following local anesthesia in a physician's clinic setting (henceforth referred to as 'in-office').

3.0 Trial Endpoints

3.1 Co-Primary Endpoints

- **Group A-Anesthesia Effectiveness:** Subject-reported pain score elicited by tympanic membrane tap following active lidocaine iontophoresis compared to sham lidocaine iontophoresis using Visual Analogue Scale (VAS).

- **Group B -Tube Placement Tolerability:** Subject-reported pain score following TDS tube placement using the VAS by subject compared to a performance goal.

3.2 Safety Endpoint

Occurrence of adverse events, by subject (Groups A and B)

3.3 Secondary Endpoints

None.

[redacted]

[redacted]

4.0 Trial Design

This study is a prospective, multicenter evaluation of safety and effectiveness of iontophoresis and tympanostomy tube placement using the IPS and TDS for TT placement for adults in an office setting.

The study will consist of two independent Groups. Each group has their own primary endpoint, each of which must pass the statistical test for the overall study to be considered successful:

- Group A will consist of 40 evaluable healthy adult subjects aged 18-50 (inclusive), enrolled at two investigational centers in the US. Group A subjects will be randomized (1:1) to receive unilateral (1 ear) treatment with either active lidocaine iontophoresis or sham lidocaine iontophoresis. The sham iontophoresis procedure will be identical to the active lidocaine iontophoresis, with the exception that the iontophoresis channel will not be activated (ie, the same drug solution will be applied to ears in both arms). After the completion of the iontophoresis, the tympanic membrane will be tapped with a dull otologic

probe to test the level of anesthesia. The subject will rate the level of pain using the VAS, and pain scores from the active iontophoresis group will be compared to the sham iontophoresis group.

- Group B will consist of 30 evaluable adults age 18 years or greater who require unilateral or bilateral tube insertion enrolled at up to 9 centers in the US. Group B subjects will receive active lidocaine iontophoresis and will have tubes placed using the TDS in all ears indicated for tube placement. The subject will rate the pain upon TDS tube insertion using the VAS, and the pain score (by subject) is compared to a fixed performance goal.

5.0 Study Cohorts

There are two cohorts in the study:

Group A: Healthy adult volunteers randomized to active lidocaine iontophoresis or sham lidocaine iontophoresis, followed by assessment of anesthesia effectiveness.

Group B: Adults indicated for tympanostomy tube placement undergoing lidocaine iontophoresis and TDS-mediated tympanostomy tube placement, followed by assessment of tube placement tolerability.

6.0 Randomization and Blinding (Group A only)

Subjects will be randomized (1:1) to either active lidocaine iontophoresis or sham iontophoresis. Randomization will be stratified by site and will be balanced by using permuted blocks. [redacted]

The study will be double-blinded such that the Investigator and subjects will be blinded to treatment assignment to minimize bias regarding Investigator and Subject-reported outcomes. [redacted]

[redacted]

7.0 Analysis Sets – Group A

7.1 Group A

7.1.1 Modified Intention to Treat (mITT)

The mITT analysis set includes all subjects who are randomized and in whom the lidocaine is introduced into the ear canal. Subjects who discontinue iontophoresis prior to the TM tap assessment or decline TM tap assessment will provide a pain score for the attempted procedure and will be included in the mITT. [redacted]

7.1.2 Per Protocol

The Per Protocol Set is a subset of the mITT and includes all mITT subjects without major protocol deviations. Major protocol deviations include:

• Eligibility violations
• Procedural deviations with the potential to affect anesthesia efficacy (eg, abbreviation of iontophoresis or use of incorrect local anesthesia drug).

7.1.3 Safety Analysis Set

The Safety Analysis Set will include all subjects in whom the lidocaine solution is introduced into the ear canal (same as mITT set).

7.2 Group B

7.2.1 Full Analysis Set (FAS)

The FAS includes all subjects in whom the lidocaine solution is introduced into the ear canal.

7.2.2 Per Protocol Set

The Per Protocol Set is a subset of the FAS and includes FAS subjects without major protocol deviations. Major protocol deviations include:

- Eligibility violations
- Procedural deviations with the potential to affect anesthesia efficacy (eg, abbreviation of iontophoresis or use of incorrect local anesthesia drug).

7.2.3 Safety Analysis Set

The Safety Analysis Set will include all subjects in whom the lidocaine solution is introduced into the ear canal (same as FAS).

8.0 Subject Disposition

The number and proportion of subjects in Groups A & B eligible for and compliant with all follow-up examinations will be presented. Subjects who withdraw from the study will be tabulated with the reasons for the withdrawal. Subjects who initiate the procedure, regardless of tolerability outcome or anesthesia effectiveness, will be encouraged to return for all follow-up assessments.

Subject disposition will be summarized for each Group with counts and percentages. Categories summarized will include the number of subjects who signed informed consent, number of screen failures (with reasons), and the number enrolled, completed, and discontinued, as well as reasons for discontinuation. The summary of disposition

will also include the number and percentage of subjects included in each analysis set described in **Section 7**.

9.0 Demographic Characteristics and Medical History

Demographic characteristics including age, sex and race/ethnicity will be descriptively summarized for all enrolled subjects in each of the defined study Groups. Significant medical history will also be summarized for all enrolled subjects in each of the defined study Groups. Demographic characteristics and medical history will be presented separately for each of the Analysis Sets defined for each Group, and by sex.

10.0 Procedure Characteristics and Device Malfunctions

Procedure and device performance characteristics will be summarized using descriptive statistics for each Group, and by treatment for Group A only.

11.0 Co-Primary Endpoint Analyses

11.1 Anesthesia Effectiveness (Group A)

This study will consist of two independent Groups, Group A and Group B. Each Group has its own primary endpoint, each of which must pass the statistical test for the overall study to be considered successful.

Group A subjects will be randomized to either active lidocaine iontophoresis treatment or sham lidocaine iontophoresis treatment. Each subject will each have a VAS score.

The null and alternative hypotheses are:

$$H_o : \mu_T - \mu_S = 0$$
$$\text{vs.}$$
$$H_1 : \mu_T - \mu_S < 0$$

where μ_T and μ_S are the mean scores in the treatment and sham arms respectively.

The primary endpoint will be evaluated in the mITT set using a permutation test at a 2.5% significance level. The primary endpoint will be demonstrated if the p-value from the permutation test is less than or equal to 0.025. These analyses will be repeated in the Per Protocol Set.

11.2 Tube Placement Tolerability (Group B)

The Group B primary endpoint is Tube Placement Tolerability defined as mean subject-reported pain score following TDS tube placement using the VAS. The mean pain score for subjects in the Group B cohort, for whom tube placement was attempted, will be evaluated against a Performance Goal pain score of 4.5.

Group B subjects will each have a VAS score that captures the pain associated with tube insertion.

The null and alternative hypotheses are:

$$H_0: \mu \geq 4.5$$
$$H_1: \mu < 4.5$$

where μ is the mean VAS score across subjects.

The primary endpoint will be evaluated in the Per Protocol set using the bootstrap method at a 2.5% significance level. The primary endpoint will be demonstrated if the upper confidence bound of a 95% non-parametric bootstrap confidence interval on the mean score is below 4.5. For bilateral subjects the highest score ('worst ear') will be used as the subject score. If a subject is intended for unilateral treatment, then the score from only the treated ear is collected and included in the analysis. Only completers, i.e., subjects with VAS scores after successful tube insertion in all indicated ears will be included in the primary analysis.

12.0 Secondary Endpoint Analyses

There are no secondary endpoints for the study.

13.0 Sample Size and Power for Primary Endpoints

13.1 Group A Primary Endpoint – Anesthesia Effectiveness

[redacted]

[redacted]

[redacted]

Twenty-four evaluable subjects in Group A will provide >95% power to detect the assumed mean difference in mean pain scores between Sham and Treatment. In order to account for uncertainty about the effect size, a total sample size of 40 is planned. Assuming 10% attrition (screen failure or withdrawn) in Group A, a sample size of 44 subjects is expected to yield an evaluable sample size of 40.

13.2 Group B Primary Endpoint – Tube Placement Tolerability

[redacted]

A sample size of 30 evaluable subjects in Group B will provide greater than 95% power at the one-sided 2.5% significance level for a non-parametric bootstrap test of the mean VAS score against a performance goal of 4.5.

14.0 Safety Endpoint Analyses

14.1 Adverse Events

Adverse events (AEs) reported during the study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting adverse events will be summarized by MedDRA system organ class and preferred term for each Group (A and B).

The frequency of each event will be summarized by seriousness, severity and by relationship to the study device, procedure and/or drug. For all AE tables, a subject reporting the same AE more than once will be counted once when calculating the number and percentage of subjects with that particular event. If a subject reports the same AE more than once or has the same AE on multiple occasions, the maximum severity grade recorded for the event will be presented.

Overall summaries of serious and non-serious AEs will be presented. The overall summaries will include the number and percentage of patients experiencing AEs classified by treatment, relationship to device/procedure/study drug, MedDRA SOC (System Organ Class) and preferred term. Summaries of AEs will also be presented by severity for each treatment group including the number and percentage of patients

experiencing AEs classified by relationship to device/procedure/study drug, SOC and preferred term.

Safety events will be reported for all subjects in which the lidocaine solution was introduced into the ear (Safety Analysis Set) and will be reported for the following time intervals:

- Events occurring during the procedure visit
- Events occurring between the procedure through the subject's final follow-up visit

[redacted]

Complete patient listings of all AEs will be provided. For each AE the following will be specified: start and stop dates, severity grade and MedDRA SOC, relationship to study device, relationship to procedure, relationship to study drug, action taken, outcome of the adverse event and seriousness, where appropriate. Any unanticipated adverse events will be noted.

14.2 Vital Signs

Descriptive statistics of mean, SD, minimum, and maximum will be presented for vital signs measurements (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, blood oxygen saturation) at all protocol-defined time points. Mean and median change from baseline to post-iontophoresis time point for each vital sign will be presented for the three protocol-defined post-iontophoresis time points (0, 30 and 60 minutes post) by treatment group. Any clinically significant change in vital sign measurements (30% or greater change from baseline) will be reported as an adverse event.

14.3 Erythema Assessment at Return Electrode Location

Erythema observed for the skin under the return electrode will be assessed by the treating physician and categorized by grade level (0 through 4) prior to and immediately after iontophoresis. Erythema findings will be summarized by number

and proportion of subjects in the Safety Analysis Set for each erythema grade level for each Group. Number and proportion of subjects reporting discomfort at the return electrode location will be summarized.

14.4 Audiometric Assessments

Change in audiometric measurements (shifts) from baseline to each follow-up visit for subjects in the Safety Analysis Set will be presented using descriptive statistics (mean, SD, median, minimum and maximum). Shifts in air conduction (AC) and bone conduction (BC) hearing thresholds will be reported for each frequency (500, 1000, 2000 and 4000 Hz) on a by-ear basis, and for each treatment arm in Group A (active or sham treatment). Shifts from baseline to each follow-up visit in air-bone gap (air conduction minus bone conduction) will also be reported for each frequency (500, 1000, 2000 and 4000 Hz) on a by-ear basis, and for each treatment arm in Group A. Shifts in air conduction pure tone average (AC PTA), bone conduction PTA (BCA) and air-bone gap averages will be presented for each follow-up time point by ear for each Group and by treatment. For all PTA measurements, the PTA will be calculated by adding the threshold levels in decibels (dB) obtained at each frequency tested divided by number of frequencies tested.

Shift tables for air conduction pure tone averages greater than 15 dB (>15dB) by ear will be calculated, and presented by ear for each Group and by treatment for each follow-up time point.

Degree of hearing loss severity will be defined according to the protocol (slight through profound) and presented by subject for each Group and by relationship to study device, procedure or study drug.

14.5 Tympanometry

Tympanometry results are used to assess of tube patency (for Group B only) and for changes in middle ear condition. Tympanometry will be performed for both ears for all subjects (Groups A and B) at screening and at all follow-up visits. The number and percentage of ears in each Group with tympanogram types A, B or C will be presented for all subjects and for each treatment arm (sham or active treatment in Group A) in the Safety Analysis Set at screening and all follow-up time points.

14.6 Otoscopic Assessments

Otoscopic examination will be performed in all ears intended for treatment at all protocol-defined time points. The number and percentage of ears in each Group with abnormal findings for the external acoustic meatus or tympanic membrane will be presented for all subjects in the Safety Analysis set for screening and all follow-up time points.

14.7 Cranial Nerve Function

Cranial nerve function physical examination will be performed for all subjects at screening, post-procedure and at all follow-up visits. The change from baseline for subjects in the Safety Analysis set in each Group will be presented for all follow-up visits.

15.0 Prior and Concomitant Medications

Prior and concomitant medications including prescription and over-the counter drugs will be recorded for Groups A and B. Medications will be coded using the World Health Organization Drug Dictionary (WHO Drug) to identify the drug class and preferred drug name.

Concomitant medications will include all medications that started on or after the procedure through the final study follow-up visit. Prior medications will include all medications that started within 28 days prior and stopped prior to the day of procedure.

Prior and concomitant medication data will be presented in a data listing for safety subjects.

[redacted]

17.0 Handling of Missing Data

Missing data and the causes of the missing data will be summarized and presented. The number and proportion of subjects eligible for and compliant with all follow-up examinations will be presented. Subjects who withdraw from the study will be tabulated with the reasons for the withdrawal. Subjects who initiate the procedure, regardless of tolerability outcome or anesthesia effectiveness, will be encouraged to return for all follow-up assessments.

Group A Primary Endpoint: If a subject in Group A discontinues iontophoresis prior to the TM tap assessment or declines TM tap assessments, the subject will provide a VAS pain score for the attempted procedure and will be included in the analysis of the primary endpoint. [redacted] Reasons for discontinuation will be documented and presented in the clinical study report.

Group B Primary Endpoint: If a subject in Group B discontinues iontophoresis or tube placement, the subject will provide a VAS pain score for the attempted procedure. Subjects with discontinued procedures will be included in a sensitivity analysis, but will not be included in the primary analysis. Only subjects with VAS scores after tubes are successfully placed in all indicated ears (one tube placed if indicated for unilateral treatment and two tubes placed if indicated for bilateral treatment) will be included in the primary analysis. If a bilateral subject has successful tube placement for one ear, but the second ear is discontinued, the higher ('worst') VAS score will be used for the sensitivity analysis. [redacted] Reasons for discontinuation will be documented and presented in the clinical study report.

[redacted]

[redacted]

[redacted]

21.0 Multiplicity Adjustment

Groups A & B each have a single primary endpoint tested at a significance level of 2.5%. Each primary endpoint must pass the statistical test for the study to be considered successful. The familywise error rate is therefore controlled at 2.5% and no multiplicity adjustments are planned.

22.0 Data Listings

Subject data will be summarized using listings and tables. All electronic case report form (eCRF) data will be listed per subject for all enrolled subjects. All listings will include the subject number and the identification of the study Group and treatment for Group A only.

23.0 Definition of Variables

23.1 Baseline

Baseline is defined as the last observation recorded prior to the treatment procedure.

Age will be calculated in years and fractions of year based on the date of informed consent relative to date of birth.

23.2 Study Day Calculation

Study Day 0 is the date of study procedure. Study Day is calculated relative to Study Day 0 and will appear in the listings where applicable.

Study Day will be calculated as:

Study Day = Date of event– Date of study procedure

Due to the acute nature of the study, no rules will be applied (eg, to assign missing day as 15th of month). Missing date data (day, month or year) will be queried.

24.0 Other General Considerations

Raw data will be presented with the exact precision that it was collected on the eCRF or other external data sources.

Percentages will be reported with exactly one decimal place. The mean and standard deviation as well as any corresponding confidence intervals will be reported with one decimal place. Blank fields on an eCRF will be displayed as blank fields in corresponding listings.

25.0 References

ICH harmonised tripartite guideline - Statistical principles for clinical trials (E9) – Step 4, 05 Feb 1998.

26.0 Appendix - Code