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; **AD**ult study to **E**valuate **P**lacement of tympanostomy **T**ubes in-office)

Study Products:

- TULA Iontophoresis System,
- 2% Lidocaine HCl/1:100,000 Epinephrine [redacted]
- and TULA Tube Delivery System

Study Phase: Pre-Pivotal

Protocol #: CPR007003
Revision: C

IDE Number: G170002

SPONSOR:
Tusker Medical, Inc.
155 Jefferson Drive, Suite 200
Menlo Park, CA 94025
USA
[redacted]

MEDICAL MONITOR:
[redacted]

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)

Protocol Number: CPR007003

Approved By:

_____ _____
[redacted]
Date

_____ _____
[redacted]
Date

_____ _____
[redacted]
Date

_____ _____
[redacted]
Date

TABLE OF CONTENTS

TABLES

FIGURES

1.0 INVESTIGATORS

A list of Investigators is provided with the Investigator's Information and will be submitted to the FDA and IRB.

Statements of Qualifications:
Qualifications of investigators are provided in the Investigator Information and will be submitted to the FDA and IRB.

2.0 STATEMENT OF COMPLIANCE

This study will be conducted in accordance with any specific provisions of the associated Institutional Review Board(s) (IRBs) and 21 CFR Parts 812 and 312. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP), ISO 14155 and the applicable national and regional regulatory requirements. Specifically, this study will be guided by the ethical principles of The Belmont Report, the Declaration of Helsinki, and the International Conference for Harmonization Good Clinical Practice (ICH-GCP).

3.0 INVESTIGATOR SIGNATURE PAGE

I acknowledge receipt of protocol and confirm I have read and understood its contents and agree to fulfill my obligations as described herein. I will ensure that the study is conducted in compliance with the protocol and all applicable regulatory requirements.

_____

INVESTIGATOR (Print Name)

_____

INSTITUTION

_____

ADDRESS

_____

SIGNATURE

_____

DATE (DD/MMM/YYYY)

4.0 LIST OF ABBREVIATIONS

AE	Adverse Event
AOM	Acute Otitis Media
CFR	Code of Federal Regulations
CRF	Case Report Form
CTA	Clinical Trial Agreement
dB	Decibels
DC	Direct Current
DIPS	Device Initiated Pause Sequence
EMLA	Eutectic Mixture of Lidocaine HCl and Prilocaine
ENT	Ear, Nose and Throat
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPS-R	Faces Pain Scale- Revised
GCP	Good Clinical Practice
HCl	Hydrochloride
ICH	International Conference for Harmonization
IDE	Investigational Device Exemption
IFU	Instructions For Use
IND	Investigational New Drug Application
IO	In Office
IPS	Iontophoresis System
IRB	Institutional Review Board
ISO	International Organization for Standardization
LCD	Liquid-Crystal Display
MedRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
MTT	Myringotomy with Tympanostomy Tube
NSR	Non-Significant Risk
OME	Otitis Media with Effusion
OR	Operating Room
PSA	Pressure-Sensitive Adhesive
SAE	Serious Adverse Event
SD	Standard Deviation
TDS	Tube Delivery System
TM	Tympanic Membrane
TT	Tympanostomy Tube
UADE	Unanticipated Adverse Device Effect
VAS	Visual Analogue Scale

5.0 PROTOCOL SUMMARY

Brief Title:	ADEPT; ADult study to Evaluate Placement of tympanostomy Tubes in-office
Working Title:	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.
IDE Protocol	IDE GI170002
Sites / Enrollment	Up to 11 investigational sites (2 Group A, up to 9 Group B) Up to 85 enrolled subjects to yield 70 evaluable subjects (40 Group A, 30 Group B).
Brief Summary:	The objectives of this 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'). This study will consist of two independent Groups, hereafter referred to as Group A and Group B. Each group has its own primary endpoint, both of which must pass the statistical test for the overall study to be considered successful and to meet the study objectives. In addition, safety will be evaluated by review of the occurrence of adverse events. The IPS will be used to facilitate anesthetic delivery to the tympanic membrane (TM). The Iontophoresis System consists of an Iontophoresis Control Unit, Iontophoresis Earsets and a return electrode patch. The Control Unit monitors and delivers a fixed amount of charge (ie, dose) to the patient through the Earsets(s) and alerts the operator when charge delivery is complete. [redacted]

	The lidocaine-based solution used for local anesthesia of the TM is 2% lidocaine HCl/ 1:100,000 epinephrine, an FDA-approved drug commercially available for other indications but is not indicated for topical administration to the TM, nor for iontophoretic administration. Therefore, the drug used in this study is considered an investigational drug for the purposes of the study. [redacted] The TDS is a mechanical device that integrates a myringotomy blade, tympanostomy tube and tube inserter for TT placement with a user-controlled activation. [redacted]
	This study will consist of two independent Groups, hereafter referred to as Group A and Group B. Each group has its own primary endpoint, both 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 years (inclusive), enrolled at two investigational centers in the US.[i] Otologic examination, cranial nerve physical exam, tympanometry and audiometry will be conducted at the screening visit. Group A subjects will be randomized (1:1) to receive unilateral treatment (1 ear) 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 current will not be activated (ie, the same drug solution will be applied to ears in both arms). After the completion of the iontophoresis procedure, 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 Visual Analogue Scale (VAS) immediately after the tap. The Investigator will also assess the level of anesthesia whether adequate for a hypothetical tube placement. Investigators and subjects will be blinded to treatment assignment. A follow-up at 3 days is required for all subjects, at which point otologic examination, cranial nerve exam, tympanometry and

[i] Subjects who are consented for the study will be considered enrolled. Throughout the protocol, enrollment numbers will reflect consented enrolled subjects with evaluable data. Enrolled subjects who are determined to be ineligible (screening failures), who withdraw prior to the study procedure or who are replaced are not included in the enrollment subject counts presented herein. Further definition of subjects included in the analysis sets is provided in Section 14- Statistical Methods

	audiometry will be conducted. If there are unresolved device, procedure or drug-related adverse events at the 3-day follow-up visit, a 12-day follow-up visit is required. 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. Otologic examination, cranial nerve physical exam, tympanometry and audiometry will be conducted at the screening visit. 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 will be compared to a performance goal. [redacted] Vital signs (diastolic and systolic blood pressure, heart rate, respiratory rate and pulse oximetry) will be monitored prior to and periodically up to 1 hour following iontophoresis. A follow-up at 3 weeks is required for all subjects, at which point otologic examination, cranial nerve physical exam, tympanometry and audiometry will be conducted.

Study Design:	Study Phase: Pre-Pivotal
	Group A: No. of Centers: 2 Number of Arms: Randomized (1:1), double-blind, sham-controlled design with two arms (active lidocaine iontophoresis vs sham lidocaine iontophoresis) Enrollment: 40 healthy adult subjects
	Group B: No. of Centers: up to 9 Number of Arms: Single arm Enrollment: 30 adult subjects requiring tympanostomy tubes
Safety Evaluations	Safety Evaluation will include the following assessments: • Otoscopic examination for visual inspection of external ear canal and TM condition at baseline, post-procedure and at the follow-up visit(s). The post-procedure exam also includes an examination of the myringotomy wound and tympanostomy tube for Group B subjects. • Audiometry to assess hearing at baseline and at the follow-up visit(s). • Tympanometry to assess tympanic membrane, middle ear conditions and tube function (Group B only) at baseline and at the follow-up visit(s). • Cranial nerve physical exam to assess cranial nerve function at baseline, post-procedure (Group B only) and at the follow-up visit(s). • Vital signs (blood pressure, oxygen saturation, respiratory and heart rates) prior to and up to one-hour following iontophoresis (Group B only). • Adverse events
Endpoints:	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 the VAS. Group B • **Tube Placement Tolerability:** Subject-reported pain score following TDS tube placement using the VAS by subject compared to a performance goal.
	Secondary Endpoints: None
	Safety Endpoint: • **Safety:** Occurrence of adverse events, by subject (both Groups A and B) [redacted]

	[redacted]
Eligibility Criteria:	Inclusion Criteria: Group A: At least one ear must meet ear-specific eligibility criteria. Group B: Each ear indicated for tube placement must meet ear-specific eligibility criteria. Group A: 1. Healthy adults, 18-50 years old at time of consent 2. Subject is able and willing to comply with the protocol and attend all study visits 3. Subject is able and willing to provide informed consent 4. Subjects with air conduction hearing thresholds of 25 dB HL or better at standard frequencies up to 2000 Hz, and 45 dB or better at 4000 Hz. 5. Subject is able to read and understand English

	Group B: 1. Adults at least 18 years of age at time of consent 2. Indication for tympanostomy tube insertion per Clinical Practice Guideline,[1] or indicated for tympanostomy tube insertion tube insertion due to barotrauma or Eustachian tube dysfunction per AAO-HNS Clinical Indicators.[2] 3. Subject is able and willing to comply with the protocol and attend all study visits. 4. Subject is able and willing to provide informed consent. 5. Subject is able to read and understand English.
	Exclusion Criteria: Group A: 1. Pregnant or lactating females. 2. Prior ear iontophoresis procedure experience. 3. Subjects with conductive hearing loss. 4. Subjects with history of sensitivity or allergic reaction to lidocaine HCl, tetracaine, epinephrine, or any hypersensitivity to local anesthetics of the amide type, or any component* of the anesthetic drug formulation. *Subjects with a known hypersensitivity to methylparaben and/or propylparaben (preservatives used in lidocaine HCl formulations), or to their metabolite para amino benzoic acid (PABA), or other components including potassium metabisulfite, sodium metabisulfite, ededate disodium or citric acid. 5. Familial history of insensitivity to lidocaine or other local anesthetics of the amide type. 6. Significantly atrophic, retracted, bimeric, monomeric or atelectatic tympanic membrane. 7. Perforated tympanic membrane. 8. Subjects with known history of ear surgery or TM condition that has the potential to affect the sensitivity of the TM (eg, prior tympanostomy tube insertion). 9. Otitis externa. 10. Damaged/denuded skin in the auditory canal. 11. Subjects with electrically sensitive support systems (eg, pacemakers, defibrillators, cochlear implants). 12. Cerumen impaction resulting in a significant amount of cleaning required to visualize the tympanic membrane. 13. Evidence of Otitis Media at day of procedure, or within the past three (3) months prior to procedure. 14. Other conditions that would preclude performing the study procedure including ear plug incompatibility.

15. Health conditions that, in the opinion of the investigator, would present undue risk to the subject, based on device/anesthetic drug product label warnings and precautions.

Group B Ear-Specific Exclusion Criteria

1. Significantly atrophic, retracted or retraction pocket at location of tube placement, bimeric, monomeric or atelectatic tympanic membrane.
2. Perforated tympanic membrane.
3. Otitis externa.
4. Hemotympanum.
5. Damaged/denuded skin in the auditory canal.
6. Cerumen impaction resulting in a significant amount of cleaning required to visualize the tympanic membrane potentially causing abrasion or irritation to the external ear canal.
7. Notable ear discomfort experienced during audiologic or otoscopic examination.
8. Anatomy that precludes sufficient visualization of and access to the tympanic membrane.
9. Anatomy that necessitates tympanostomy tube placement in the posterior half of the tympanic membrane.

Group B General Exclusion Criteria

10. Pregnant or lactating females
11. History of sensitivity or allergic reaction to lidocaine HCl, tetracaine, epinephrine, or any hypersensitivity to local anesthetics of the amide type, or any component* of the anesthetic drug formulation.

    *Subjects with a known hypersensitivity to methylparaben and/or propylparaben (preservatives used in lidocaine HCl formulations), or to their metabolite para amino benzoic acid (PABA), or other components including potassium metabisulfite, sodium metabisulfite, ededate disodium or citric acid.

12. Familial history of insensitivity to lidocaine or other local anesthetics of the amide type.
13. Electrically sensitive medical support systems (eg, pacemakers, defibrillators, cochlear implants)
14. Other conditions that would preclude performing the study procedure including iontophoresis system ear plug incompatibility.
15. Health conditions that, in the opinion of the investigator, would present undue risk to the subject, based on device/anesthetic drug product label warnings and precautions.

Sample Size and Power	Group A: A sample size of 40 subjects will provide greater than 95% power at the one-sided 2.5% significance level for a permutation test on the difference in mean VAS scores between the two arms. The null and alternative hypotheses are: $H_0: \mu_T - \mu_S = 0$ $H_1: \mu_T - \mu_S < 0$ Group B: A sample size of 30 subjects will provide greater than 95% power at the one-sided 2.5% significance level for a bootstrap test of the mean VAS score against a performance goal of 4.5. The null and alternative hypotheses are: $H_0: \mu \geq 4.5$ $H_1: \mu < 4.5$

6.0 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

6.1. Clinical Program Overview

Tusker Medical has developed a suite of technologies designed to enable in-office placement of tympanostomy tubes in pediatric and adult patients. This protocol (CPR007003) describes two groups of adult subjects, each designed to demonstrate a particular aspect of the investigational technology. [redacted]

Although this study is conducted in adult subjects and the investigational technology will ultimately be available for both adult and pediatric patients, it is anticipated that the majority of use will be in the pediatric population. Therefore, **Section 6.2** is focused on the ultimate use of the product in the pediatric population.

6.2. Clinical and Technology Background

Otitis media (inflammation of the middle ear) is the most frequent diagnosis in sick children visiting pediatrician offices. Seventy-five percent of children experience at least one episode of otitis media by their third year.[3]

Otitis media has several variations, including acute otitis media (AOM) and otitis media with effusion (OME). AOM is characterized by acute signs and symptoms of middle ear inflammation or infection. OME is characterized by the presence of fluid in the middle ear with or without signs or symptoms of acute ear infection. The highest incidence of AOM occurs between six and 24 months of age and declines until a small reversal is seen between five and six years of age, at the time of school entry.[4] There tends to be a higher incidence of OME in younger than in older children, because the Eustachian tube in younger children is shorter, narrower, and more horizontal and the immune system is less developed compared to older children or adults. There is also increased incidence of OME associated with craniofacial anomalies, cleft palate, and Down syndrome. Middle ear effusion can result in temporary conductive hearing loss and negatively impact a child's cognitive, language, and emotional development.

More than 750,000 tympanostomy tube procedures are performed in children younger than age 18 annually in the US to address recurrent AOM or OME, making it one of the most common surgical procedures performed in children.[5] By age 3, almost 7% of all children will have tympanostomy tubes.[1] Over 75% of tympanostomy tube procedures in the US are performed for children 12 years or younger, with 58% of tube procedures for children less than 5 years of age.[5] Over 95% of tympanostomy tube insertion procedures in children are performed in the operating room (OR) under general anesthesia.[5]

The typical Myringotomy with Tympanostomy Tube placement (MTT) procedure in a child involves the following sequence of events:

- The child fasts from the evening before the procedure and is brought to the hospital or ambulatory surgery center.
- Premedication with oral midazolam may be provided to calm the child prior to parental separation.[6]
- After general anesthesia is attained, prophylactic analgesia to address post-operative pain such as rectal acetaminophen or intranasal fentanyl is typically provided.[7]
- Cerumen clearance is performed.
- Using a myringotomy blade, an adequately sized myringotomy incision is then made, typically in the anteroinferior portion of the tympanic membrane.[8,9]
- Fluid may be removed from the middle ear space using suction.
- Using alligator forceps, the tympanostomy tube is manipulated and tucked into the myringotomy incision.
- Minor adjustments are then often performed using standard otologic microinstruments, such as a Rosen needle or alligator forceps, to achieve optimal tube position.[10]
- Multiple attempts to place the tube may be required in a considerable number of cases.[8]

In adult patients and older children, tympanostomy tubes can be placed in an office setting using a variety of local anesthesia options although none are indicated for anesthesia of the ear drum. Phenol (carbolic acid) is often used to cause a partial thickness chemical burn with tissue necrosis, which leads to localized anesthesia of the TM.[11] Other anesthetics, such as EMLA cream (Eutectic Mixture of Local Anesthetics, lidocaine 2.5% and prilocaine 2.5%), lidocaine HCl injections and Bonain's Solution (cocaine hydrochloride, menthol, phenol) and tetracaine injections are used less frequently.[12,13,14] None of the local anesthetics employed in adults are regularly used with small children, as they are all associated with discomfort or a lengthy onset incompatible with pediatric use.

There are several potential advantages to providing otolaryngologists, or Ear, Nose and Throat (ENT) surgeons, with technology that enables in-office tube placement in pediatric patients. The perioperative risks associated with the general anesthesia required for tube placement in the OR can be avoided with an office-based procedure. General anesthetic complications occur at measurable rates ranging between 12.6% and 18% in tube procedures in children.[15,16] Although serious adverse effects of general anesthesia during tube procedures are uncommon, they can be severe including laryngospasm, airway obstruction, desaturation, dysrhythmia and post-operative vomiting requiring treatment.

In addition, there is an increasing interest in gaining a better understanding of the potential for neurodevelopmental impact of general anesthesia in small children. A growing body of literature suggests a linkage between general anesthesia exposure and neurodevelopmental impact, though it remains difficult to separate the post-general anesthesia outcomes from the underlying condition for which the child underwent surgery. One study showed that children who received general anesthesia before age 3 years were approximately 1.9 times as likely as controls to show language disability and 1.7 times as

likely to show cognitive disability, even after a single anesthetic exposure.[17] In another study, children with a history of multiple exposures to general anesthesia before 4 years of age were shown to have a significantly increased risk of developing learning disabilities compared to those who had a single exposure or none.[18] FDA recently issued a Drug Safety Communication warning that repeated use of general anesthetic and sedation drugs in young children may affect the development of children's brains.[19]

In addition, both pre-operative anxiety and post-operative stress behaviors are common in children. A reported 50-75% of children who undergo general anesthesia develop significant behavioral stress before surgery.[20] In a study of children undergoing hernia repair, tympanostomy tube placement, tonsillectomy, adenoidectomy other otolaryngologic and minor procedures, it was reported that up to 54% of children exhibit maladaptive behavior responses following surgery including general anxiety, enuresis, separation anxiety and temper tantrums at 2 weeks postoperatively, with up to 47% reporting sleep problems.[21] Up to 57% of children undergoing anesthesia with sevoflurane show emergence delirium, defined as at least 3 minutes of thrashing requiring restraint.[22]

Tusker Medical has two technologies developed with the intent to enable safe and reliable placement of tympanostomy tubes in pediatric patients in an office setting with localized administration of anesthetics to the tympanic membrane.[ii] The technologies thus provide the capability to potentially reduce the risks and side effects of general anesthesia, reduce the patient and parental anxiety that can be associated with OR-based pediatric procedures, and move procedures to a lower cost setting.

The two technologies consist of a Tube Delivery System (TDS) and an Iontophoresis System (IPS). The TDS is a mechanical device that rapidly performs a myringotomy and delivers a preloaded tympanostomy tube with single-button actuation. The IPS is a single-use microprocessor-controlled direct current (DC) generator used prior to the TDS to facilitate anesthesia of the tympanic membrane by driving ions of a drug solution into the tissue.

7.0 STUDY DEVICES

[redacted] The Iontophoresis System consists of an Iontophoresis Control Unit, Iontophoresis Earsets and a return electrode patch. The Control Unit monitors and delivers a fixed amount of charge (ie, dose) to the patient through the Earsets(s) and alerts the operator when charge delivery is complete. [redacted] If the Reduce feature is used by the operator, the device tracks overall charge, ensuring total charge/dose delivered remains the same as

[redacted]

the prior generation of the device. [redacted]

[redacted]

Tusker Medical, Inc. has a Tube Delivery System intended to provide a means to create a myringotomy with insertion of a preloaded tympanostomy tube. The design and operation of the TDS is intended to standardize the surgical approach to tympanostomy tube placement whereby upon actuation of the TDS, a myringotomy is created and a Tusker Medical tympanostomy tube is placed nearly simultaneously (within 500 ms). The TDS device combines myringotomy creation and tube insertion into one straightforward procedure step, thus avoiding the need to pass an exposed surgical blade though the ear canal of an awake and mobile patient.

[redacted]

7.1. Device Descriptions

7.1.1. Iontophoresis System

Iontophoresis uses low-level electric current to direct movement of drug ions into tissue through skin or mucosal surfaces. [redacted] The IPS employs a low-level electric current to transport the ionic drug, and may be performed unilaterally or bilaterally. The IPS is battery-powered and delivers 6.4mA-minutes of charge at a current of 0.8 mA (maximum) to each channel.

The IPS is a single use device and consists of three components: an Iontophoresis Control Unit, Iontophoresis Earsets and a Return Electrode Patch. For bilateral drug delivery, two Iontophoresis Earsets are required. Accessories to the Iontophoresis System include a Syringe and Earset Sizers. All components of the IPS are provided non-sterile and no sterilization is required. All patient contact materials have been assessed for biocompatibility per ISO 10993. Iontophoresis with the IPS may be performed unilaterally or bilaterally, and bilateral iontophoresis may be performed either sequentially or simultaneously.

- The **Earset Sizers** are used to determine the Earset size that best fits the patient's anatomy. They are color-coded to correspond to each Earset size. Consecutive sizes are mounted at each end of a handle and labeled with a size number (Size 1 through Size 6). They are a reusable accessory required to determine the Earset size for the ear canal requiring treatment.

- The **Earset** includes an Ear Plug with Pressure-Sensitive Adhesive (PSA) attached to a handle, an integrated fill system, an electrical connector, and an integrated ear electrode through which electrical current is delivered to the drug solution. The integrated fill system allows for the administration of drug solution with the electrode in situ for the initial fill of the external ear canal and for the intra-procedure delivery of additional drug solution to the external ear canal, as needed. Multiple Earset sizes are available to accommodate variation in patient anatomy and are color-coded to correspond to the Earset Sizers. The range of ear plug sizes is appropriate for both pediatric and adult patients.

- The **Control Unit** provides two independent channels of electrical current to the solution in the ear canal and to a single shared return electrode patch. The Control Unit monitors and delivers a fixed amount of charge and alerts the operator when current delivery is complete.

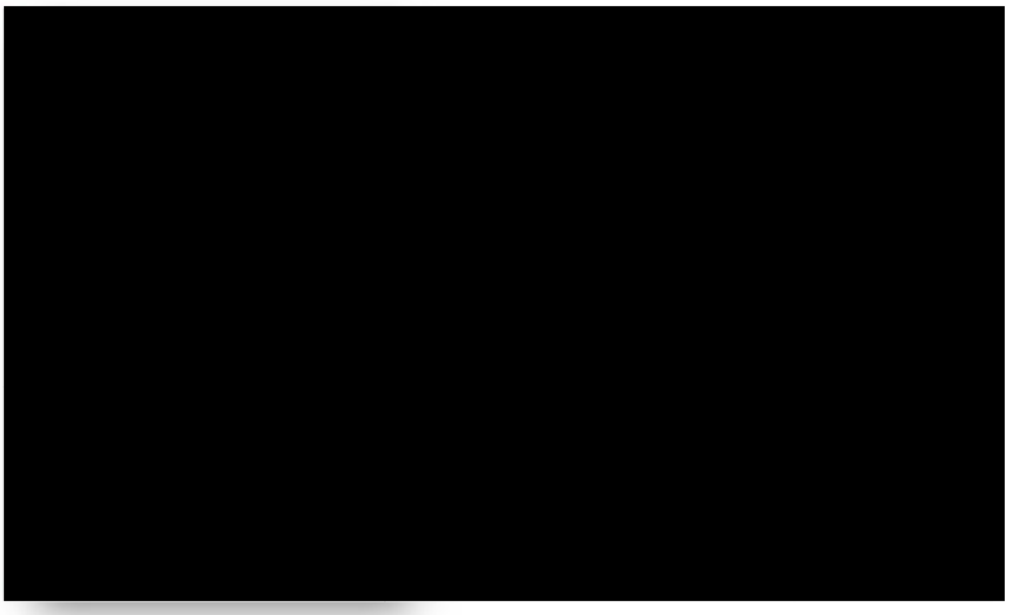
- The **Return Electrode Patch** attaches to the patient's skin at a location remote from the ears to complete the electrical circuit and is connected to the Earset and Control Unit via the return electrode snap.

- The **Syringe** is a single use device that allows for administration of drug solution through the Earset into the ear canal.

Iontophoresis Control Unit

[redacted] The *Control Unit* provides two independent channels of electrical current. It is connected to one or two *Earsets* and the *Return Electrode Patch* via the electrical connectors and return electrode snap, respectively. The *Control Unit* can deliver current to a patient's left and right ears sequentially or simultaneously, if desired. The *Control Unit* includes embedded software that delivers and regulates both current and accumulated charge and alerts the operator when current delivery is complete. [redacted]

The user interface with the *Control Unit* consists of two push buttons and a visual indicator of cycle progress (progress bars). Each push button is used to independently operate one *Earset*. Each push button can start, pause or resume current to one *Earset*. Push buttons are color coded (Yellow and Blue) to identify the *Earset* side they control. The progress bars are used to monitor iontophoresis progress and alert the operator of various device states. [redacted] If the Reduce feature is used by the operator, the device tracks overall charge, ensuring total charge/dose delivered remains the same as the prior generation of the device.

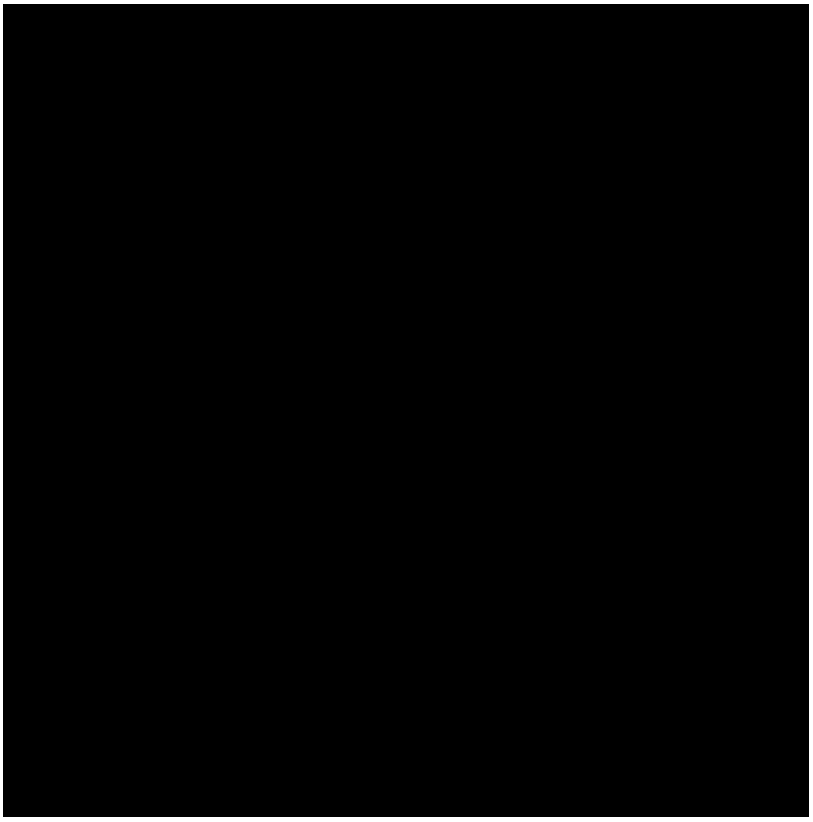


Iontophoresis Earset

The Iontophoresis Earset *(Earset)* is shown in **Figure 2**. It includes an ear plug attached to a handle, an integrated fill system, and an integrated electrode and cable through which electrical current is delivered to the drug solution. The ear plug provides a seal to keep the drug solution in the ear canal. The surface of the ear plug is coated with a soft pressure sensitive skin adhesive that secures it in the ear canal during the procedure and helps maintain a seal during the procedure. The PSA is partially covered by a protective liner to facilitate placement of the ear plug in the ear canal. This liner is peeled off once the ear plug is in place. A soft pressure applicator mounted inside the ear plug enables circumferential adhesion of the PSA coated ear plug to the ear canal surface by allowing the user to apply pressure by moving the handle. The ear plug also incorporates a peel flap feature, which is used to peel the adhering ear plug off the ear canal surface at the end of the procedure. Six color-coded Earset sizes are available to accommodate variation in ear canal size. For bilateral drug delivery, two Earsets are required.

The integrated fill system allows for the administration of a drug solution to the ear canal, as needed. At one end, the integrated fill system contains a central fill lumen with a blunt tip through which the drug solution may be administered. At the other end of the integrated fill system, a standard luer lock enables mating with the included *Syringe*. The handle of the *Earset* includes a vent that allows air and excess fluid to escape during delivery of fluids to the ear canal. The electrical cable and fill system tubing are coiled together, and a clip is provided to secure the tubing to the patient's clothing, and thereby allow for routing behind the patient's ear.

The *Earset* also includes an integrated ear electrode. The integrated ear electrode is used to deliver positive DC electrical current to the administered drug. [redacted]



Return Electrode Patch

The Return Electrode Patch (*Return Electrode*) shown in **Figure 3**, attaches to the patient's skin, generally on the arm or back, to complete the electrical circuit. The Return Electrode contains a hydrogel, which contacts and adheres to the patient's skin. The Return Electrode acts as a cathode. The Return Electrode is connected to the System Cable of the Control Unit.

Figure 3. Return Electrode Patch

Syringe

The *Syringe* is a standard 10 cc syringe with a compatible Luer Lock tip.

Earset Sizer

The *Earset Sizers*, shown in **Figure 4**, come in six sizes (Size 1 through Size 6). This accessory is utilized to determine the *Earset* size for each ear canal. Each *Earset* has a corresponding *Earset Sizer* of the same color.

Consecutive sizes are mounted at each end of the handle and labeled with the appropriate size number (Size 1 through Size 6). They are a reusable accessory required to determine the Earset size for the ear canal requiring treatment.

Figure 4. Ear Plug Sizers

Iontophoresis System Safety Features

There are several design features of the IPS to ensure safety:

- The current delivery is limited by one software control (delivery tolerance) and one hardware control (current limiter) that is independent of software.

[redacted]

- The electrode is housed completely inside the ear plug, greatly reducing the possibility of burns caused by direct contact between the electrode and skin.

- The return electrode has a large surface area, which decreases current density and reduces skin irritation potential. [redacted]

- The ear plug handle contains a vent designed to prevent ear canal over-pressurization during filling.

- [redacted]

7.1.2. Iontophoresis Basic Operating Principles

Subject Preparation

The otolaryngologist will perform a standard ear cleaning to remove cerumen that may affect the ability of the investigator to visualize the TM or affect the ability of the drug solution to contact the TM. The otolaryngologist will inspect the TM under an operating microscope to ensure there is no TM perforation that would permit drug into the middle ear, and to ensure no other contraindications related to TM condition are present. Note that a pre-study tympanogram will also serve as an additional mechanism to eliminate subjects with a TM perforation.

Drug Instillation

First, the otolaryngologist uses the *Earset Sizers* to select the appropriate *Earset* size for the ear canal requiring treatment. The otolaryngologist then places the ear plug portion of the selected *Earset* into the ear canal. Once the ear plug is positioned, the otolaryngologist gently removes the protective liner, exposing the PSA to the ear canal. Using the device handle, circumferential pressure is applied through the ear plug, against the surface of the ear canal ensuring adhesion of the PSA. The otolaryngologist then routes the coiled cable behind the ear and attaches the clip to the patient's clothing. The Earset's integrated fill system is used to instill the selected drug into the external ear canal. A typical adult ear canal, including the Earset reservoir, will accommodate approximately 1-2 cc's of fluid. The otolaryngologist repeats the process if required for the second ear and connects the Earset/Earsets and Return Electrode Patch to the System Cable connected to the Control Unit. The Return Electrode Patch is adhered to the patient's skin, typically on the back of the neck or the arm.

Subsequently, the Control Unit is turned on by removing the battery pull tab. Iontophoresis is started by pressing the appropriate left or right buttons on the Control Unit. After a current ramp-up period, a direct current of up to 0.8 mA is administered (schematic in

Figure 5). During this time, the direct current transports the drug into the tympanic membrane tissue (schematic in **Figure 6**). Current delivery is then completed with a ramp-down period. The entire current delivery period lasts approximately 10 minutes. The Control Unit allows the user to initiate, pause, or resume current delivery from the Control Unit at any time. [redacted] The new control unit model includes an added 'Reduce' feature to allow the user to optionally and temporarily reduce the current level by 25% if a subject experiences discomfort during iontophoresis. If the Reduce feature is used by the operator, the device tracks overall charge ensuring total charge/dose delivered remains the same as the prior generation of the device. During Iontophoresis, the otolaryngologist may use the *Earset's* integrated fill system to fill additional drug into the ear canal, if leak of solution has occurred.

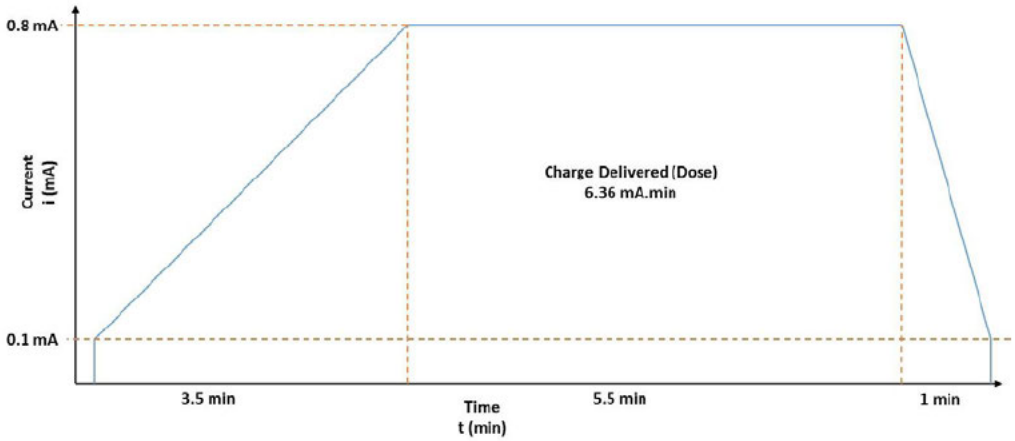


Figure 5. Current Ramp Profile

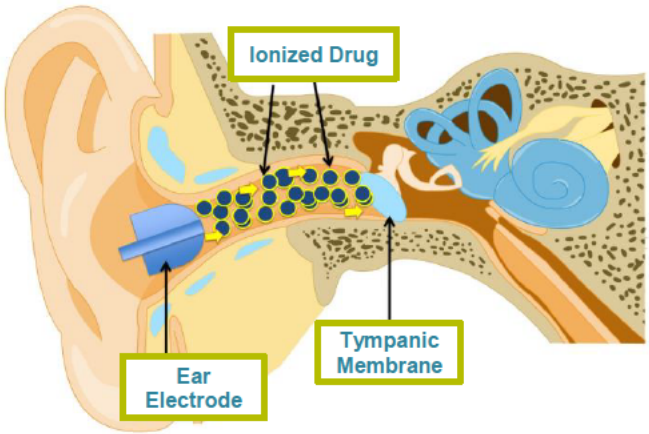


Figure 6. Schematic of Iontophoresis of the TM

Drug Removal

After Iontophoresis is completed, the *Earsets* and *Return Electrode Patch* are removed from the patient. The *Earset* is removed by using the ear plug peel flap and the anesthetic solution is removed from the ear canal either by wick, tilting or suctioning. The IPS is designated for a single-use only, with the exception of the *Earset Sizers*, which are reusable.

7.1.3. Tube Delivery System (TDS)

The TDS is a mechanical device that creates a myringotomy and inserts the Tusker Medical Tympanostomy Tube with a single-button controlled activation. It is intended to provide a means to create a myringotomy with insertion of a preloaded Tympanostomy Tube (Grommet-type, see **Figure 7**). The TDS incorporates design features intended to facilitate tube placement in-office including rapid tube placement and elimination of exposed sharps during insertion or retraction of the device in the ear canal.

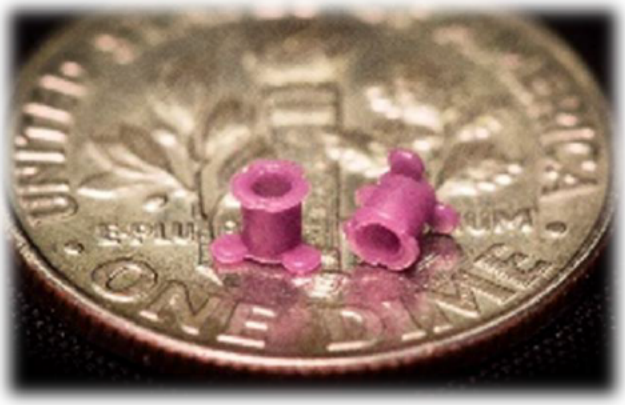


Figure 7. Tusker Medical Tympanostomy Tube

[redacted]

The TDS is provided to the physician with one pre-loaded Tusker Medical Tympanostomy Tube. It is provided sterile and for single-use only. **Figure 8** provides a graphic representation of the TDS.

Figure 8. Tube Delivery System

To use the device, the physician positions the blunt tip of the device, under microscopic guidance, against the tympanic membrane at the intended myringotomy site. Upon actuation of the device, the TDS performs the following actions in sequence in less than 500msec:

1) *Myringotomy*: the cutter extends a fixed distance (maximum of 3 mm) to create an incision in the tympanic membrane;

2) *TT placement across the tympanic membrane:* [redacted]
3) *Retraction:* [redacted] facilitating atraumatic removal of the TULA TDS from the external acoustic meatus.

Following tube deployment, the physician may make minor adjustments to final tympanostomy tube position in the tympanic membrane if required using standard otologic microinstruments, such as a Rosen needle or alligator forceps, to achieve optimal tube position as is commonly performed with any tube placement procedure.[10]

8.0 STUDY DRUG

The iontophoresis will be performed using 2% lidocaine HCl/1:100,000 epinephrine [redacted] anesthetic drug solution. [redacted] The formulation of the drug solution is provided in the corresponding package insert. General pharmacology, toxicology and pharmacokinetics, local toxicity, and ototoxicity information regarding lidocaine and epinephrine, as well as prior human experience with the drug and iontophoretic route of administration is provided in the Investigator Brochure.

[redacted]

[redacted]

9.0 TUSKER MEDICAL CLINICAL EXPERIENCE

[redacted]

The Investigator's Brochure (CIB007001) includes a complete summary of the prior clinical data and the specific device generations used for each study.

10.0 RISK AND BENEFIT ANALYSIS

A description of risks and an analysis of risk versus benefit for subjects undergoing iontophoresis with tube placement (Group B) is presented in the Investigator's Brochure CIB007001. Group A subjects consist of healthy adult volunteers. There are no benefits to healthy volunteers. However, the information collected will provide a foundation for the development of future applications and technology.

11.0 STUDY DESIGN

11.1. Study Objective

Prior clinical trial experience has provided preliminary safety and effectiveness of in-office tympanostomy tube placement in children using the Tusker Medical TULA Iontophoresis and Tube Delivery Systems. The objectives of this 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.

This study will consist of two independent Groups (Group A and Group B). Each group has its own primary endpoint, both of which must pass the statistical test for the overall study to be considered successful and to meet the study objectives. In addition, safety will be evaluated by review of the occurrence of adverse events.

The data from this study will provide evidence that the investigational system will provide anesthesia sufficiently effective for the placement of tympanostomy tubes. [redacted]

11.2. Overall Study Design – Groups and Enrollment

This study is 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.

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. The two Groups may be enrolled in parallel, and investigational sites may enroll subjects in Group A alone, Group B alone, or both Groups.

Group A will consist of 40 healthy adult subjects aged 18-50 with evaluable data, enrolled at two investigational centers in the US. Otologic examination, cranial nerve physical exam, tympanometry and audiometry will be conducted at the screening visit.

Group A subjects will be randomized to receive unilateral treatment (1 ear) 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). [redacted]

After the completion of the iontophoresis, the tympanic membrane will be touched with a dull otologic probe to test anesthesia effectiveness. The touch to the TM will slightly deflect the TM and allow for an assessment of anesthesia effectiveness. The touch is referred to as a 'tap' throughout the protocol. [redacted] The subject will rate the level of pain using the Visual Analogue Scale (VAS) after the tap. [redacted] Investigators and subjects will be blinded to treatment assignment.

A follow-up at 3 days post-procedure is required for all subjects, at which point otologic examination, cranial nerve exam, tympanometry and audiometry will be conducted. If there are unresolved device, procedure or drug-related adverse events at the 3-day follow-up visit, a 12-day follow-up visit is required.

Group B will consist of 30 adults 18 years or older who require unilateral or bilateral tube insertion, enrolled at up to 9 centers in the US. Otologic examination, cranial nerve physical exam, tympanometry and audiometry will be conducted at the screening visit.

Group B subjects will receive active lidocaine iontophoresis and TDS-mediated tube placement in all ears that require tube insertion. The VAS score will be collected *after* any manipulations required to place the tube so that the pain score fully reflects the activities required to place the tube. VAS score will be collected for each ear undergoing tube placement. If a subject discontinues iontophoresis or the procedure prior to tube placement with the TDS, a VAS score will be collected for the attempted procedure. The pain score will be compared to a fixed performance goal.

Vital signs (diastolic and systolic blood pressure, heart rate, respiratory rate and pulse oximetry) will be monitored 15 minutes and immediately prior to iontophoresis, immediately following the iontophoresis, following tube placement, 30 minutes and 60 minutes after completion of iontophoresis for all Group B subjects.

A follow-up at 3 weeks is required for all subjects, at which point an otologic examination, cranial nerve exam, tympanometry and audiometry will be conducted.

11.2.1. Enrollment Limits

Group A: Group A consists of 2 sites. Each site may enroll no greater than 70% of Group A subjects.

Group B: Group B consists of up to 9 sites. Each site may enroll no greater than 30% of Group B subjects.

11.3. Primary Endpoint Rationale

Group A: Anesthesia Effectiveness (Subject-Reported)

In Group A, active lidocaine iontophoresis will be compared to sham lidocaine iontophoresis (ie, lidocaine in the ear canal but without activating the iontophoresis unit for that channel). After iontophoresis/sham treatment is complete, the subject will use the VAS to rate the pain associated with a single tympanic membrane tap using a standardized blunt otologic probe. The VAS was selected because it is a validated self-report pain instrument commonly used in research settings with adults (reviewed in Jensen and Karoly).[34] The VAS is validated for use in subjects 8 years of age and older (reviewed in Stinson et al (2006).[35] The VAS consists of a 10 centimeter (cm) line with a statement at each end representing the extreme limits of pain intensity ("No pain" to "Worst possible pain"). The subject reports their pain intensity by making a mark along the line and the line is measured to convert the subject response to numeric score (0-10 in centimeters).

[redacted]

Group B: Tube Placement Tolerability

The goal of Group B is to demonstrate that the pain associated with tube insertion using the TDS after lidocaine iontophoresis provided by the IPS will be tolerable for pediatric subjects. [redacted] In Group B, ears indicated for tympanostomy tubes will receive active lidocaine iontophoresis and tympanostomy tube insertion using the TDS, and the pain associated with tube insertion will be collected using the VAS. The mean VAS score will be compared to a performance goal (PG).

[redacted] Jensen et al (2003) re-analyzed 2 randomized controlled trials of postoperative pain for adults using VAS (N=123 and N=125).[39] They determined

cut points for pain severity as no pain at 0 to 4 mm, mild pain 5 to 44 mm, moderate pain 45 to 74 mm and severe pain 75 to 100mm. Altogether, the literature reports show remarkable consistency for the experimentally-determined cut point between mild and moderate pain.

Prior TULA in office tube delivery study results indicate that tolerability scores are anticipated to be in the mild range. Therefore, it is reasonable to set a performance goal to be superior to (less painful than) moderate pain. Using the VAS, Tusker will demonstrate superiority to a score of 4.5cm (or 45mm), based on Jensen's determined cut point of 45mm for adult VAS scores, showing that the pain associated with in-office tube insertion in adult subjects is mild.

11.4. Study Population

Group A will consist of 40 healthy adult volunteers and Group B will consist of 30 adults indicated for tympanostomy tubes in one or both ears. The study may enroll up to 85 subjects to achieve 40 subjects with evaluable data in Group A and 30 subjects with evaluable data in Group B, allowing for approximately 15 screen failure or withdrawn subjects.

11.4.1. Definition of Enrollment

All subjects who consent for participation in the study are considered enrolled. Subjects who do not meet eligibility criteria are considered screen failures. **Section 14.0** Statistical Methods provides further definition of subjects included in the analysis sets.

11.5. Primary Endpoints

There are two primary endpoints for the study, one for Group A and one for Group B. Both primary endpoints must be achieved for the trial to be considered successful.

Primary endpoint for Group A:

Anesthesia Effectiveness: subject-reported pain score elicited by tympanic membrane tap following active lidocaine iontophoresis compared to sham lidocaine iontophoresis using the VAS.

Each Group A subject will each have a VAS score. If a subject in Group A discontinues iontophoresis prior to the TM tap assessment or declines the TM tap assessment, the subject will provide a 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.

Randomization will assign subjects to either unilateral active lidocaine iontophoresis or unilateral sham lidocaine iontophoresis treatment. Both the subject and the investigator

performing the taps will be blinded as to treatment assignment. Blinding is further described in **Sections 12.5.5 and 14.3.1**.

A single tap will be performed on the treated (or sham-treated) ear using a standardized dull otologic probe on the anterior part of the tympanic membrane. [redacted]

Primary endpoint for Group B:

Tube Placement Tolerability: Subject-reported pain score following TDS tube placement using the VAS.

Group B subjects will each have a single subject-level VAS score that reflects the pain associated with tube insertion; if both ears are treated the highest score of the two ears will serve as the subject-level score. The statistical test for the primary endpoint is a hypothesis test comparing mean VAS score to a performance goal of 4.5, as described in **Section 11.3**.

Group B subjects may require unilateral or bilateral tubes and will receive active lidocaine iontophoresis and tube placement using the TDS in each ear that requires a tube insertion.

[redacted]

The VAS score will be collected *after* any manipulations required to place the tube so that the pain score fully reflects the activities required to place the tube. A VAS score will be reported for each ear undergoing tube placement, and the highest (worst) pain reported by the subject will be used as the unit of analysis.

If a subject in Group B discontinues iontophoresis or tube placement, the subject will provide a VAS pain score for the attempted procedure. [redacted]Reasons for discontinuation will be documented and presented in the clinical study report.

11.6. Safety Endpoint

Safety: The occurrence of all adverse events, by subject. The totality of the safety data will be summarized and presented. Safety events will be reported for all subjects in which the lidocaine solution was introduced into the ear (see **Section 14.2.3**), 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

Safety data will be presented separately as follows:

- Group A
- Group B

11.7. Secondary Endpoints

There are no formal tests of hypotheses for secondary endpoints in either Group A or Group B.

[redacted]

[redacted]

11.9. Inclusion Criteria

Group A: At least one ear must meet ear-specific eligibility criteria.
Group B: Each ear indicated for tube placement must meet ear-specific eligibility criteria.

Group A:

1. Healthy adults, 18-50 years old at time of consent
2. Subject is able and willing to comply with the protocol and attend all study visits
3. Subject is able and willing to provide informed consent
4. Subjects with air conduction hearing thresholds of 25 dB HL or better at standard frequencies up to 2000 Hz, and 45 dB or better at 4000 Hz.
5. Subject is able to read and understand English

Group B:

1. Adults at least 18 years of age at time of consent
2. Indication for tympanostomy tube insertion per Clinical Practice Guideline,[40] or indicated for tympanostomy tube insertion tube insertion due to barotrauma or Eustachian tube dysfunction per AAO-HNS Clinical Indicators[41]
3. Subject is able and willing to comply with the protocol and attend all study visits
4. Subject is able and willing to provide informed consent.
5. Subject is able to read and understand English.

11.10. Exclusion Criteria

Group A:

1. Pregnant or lactating females.
2. Prior ear iontophoresis procedure experience.
3. Subjects with conductive hearing loss.
4. Subjects with history of sensitivity or allergic reaction to lidocaine HCl, tetracaine, epinephrine, or any hypersensitivity to local anesthetics of the amide type, or any component* of the anesthetic drug formulation.

   *Subjects with a known hypersensitivity to methylparaben and/or propylparaben (preservatives used in lidocaine HCl formulations), or to their metabolite para amino benzoic acid (PABA), or other components including potassium metabisulfite, sodium metabisulfite, ededate disodium or citric acid.
5. Familial history of insensitivity to lidocaine or other local anesthetics of the amide type.

6. Significantly atrophic, retracted, bimeric, monomeric or atelectatic tympanic membrane.
7. Perforated tympanic membrane.
8. Subjects with known history of ear surgery or TM condition that has the potential to affect the sensitivity of the TM (ex. prior tympanostomy tube insertion)
9. Otitis externa.
10. Damaged/denuded skin in the auditory canal.
11. Subjects with electrically sensitive support systems (pacemakers, defibrillators, etc.).
12. Cerumen impaction resulting in a significant amount of cleaning required to visualize the tympanic membrane.
13. Evidence of Otitis Media at day of procedure, or within the past three (3) months prior to procedure.
14. Other conditions that would preclude performing the study procedure including ear plug incompatibility.
15. Health conditions that, in the opinion of the investigator, would present undue risk to the subject, based on device/anesthetic drug product label warnings and precautions.

Group B:

1. Significantly atrophic, retracted or retraction pocket at location of tube placement, bimeric, monomeric or atelectatic tympanic membrane.
2. Perforated tympanic membrane.
3. Otitis externa.
4. Hemotympanum.
5. Damaged/denuded skin in the auditory canal.
6. Cerumen impaction resulting in a significant amount of cleaning required to visualize the tympanic membrane potentially causing abrasion or irritation to the external ear canal.
7. Notable ear discomfort experienced during audiologic or otoscopic examination.
8. Anatomy that precludes sufficient visualization of and access to the tympanic membrane.
9. Anatomy that necessitates tympanostomy tube placement in the posterior half of the tympanic membrane).

General Exclusion Criteria

10. Pregnant or lactating females.
11. History of sensitivity or allergic reaction to lidocaine HCl, tetracaine, epinephrine, or any hypersensitivity to local anesthetics of the amide type, or any component* of the anesthetic drug formulation.

    *Subjects with a known hypersensitivity to methylparaben and/or propylparaben (preservatives used in lidocaine HCl formulations), or to their metabolite para amino benzoic acid (PABA), or other components including potassium metabisulfite, sodium metabisulfite, ededate disodium or citric acid.

12. Familial history of insensitivity to lidocaine or other local anesthetics of the amide type.
13. Electrically sensitive medical support systems (eg, pacemakers, defibrillators, cochlear implants)

14. Other conditions that would preclude performing the study procedure including iontophoresis system ear plug incompatibility.
15. Health conditions that, in the opinion of the investigator, would present undue risk to the subject, based on device/anesthetic drug product label warnings and precautions

If a previously-determined eligible subject presents on the procedure day with a change in condition, such as an acutely infected ear, the investigator may use clinical judgment to determine whether the condition as presented precludes performing the study procedure (Group B Exclusion 14). The physician also has the option to re-schedule the procedure if the condition is transient.

12.0 STUDY PROCEDURES

12.1. Investigator Training

Investigators will be asked to refer to the drug package insert, device Instructions For Use (IFU) and the Investigator's Brochure (CIB007001) for risks related to procedure, drug and device. The Investigators will be trained on use of the Iontophoresis and Tube Delivery Systems using a model system.

12.2. Evaluation Methods

12.2.1. Diagnosis (Group B)

Eligible subjects will be indicated for tympanostomy tube placement in alignment with the Clinical Practice Guideline.[1] The Clinical Practice Guideline for tympanostomy tubes in children was developed by a multidisciplinary panel, to provide clinicians with evidence-based recommendations on patient selection and surgical indications for and management of tympanostomy tubes in children.

In addition to indications aligned with the Clinical Practice Guideline for children, the adult subjects in Group B with barotrauma or Eustachian tube dysfunction may also be indicated for tube placement per AAO-HNS Clinical Indicators (2010).[2]**Error! Bookmark not defined.**

According to the Clinical Practice Guideline, the decision to perform unilateral or bilateral tympanostomy tube insertion when unilateral OME is present should be based on caregiver preference [to accept or decline the risk of a second surgical procedure] and the likelihood of persistent OME developing in the opposite ear. For AOM with presence of effusion, the Guideline recommends bilateral TT placement for unilateral or bilateral disease. With the current care paradigm, a physician may perform bilateral tube placement for a unilateral condition to avoid the risk of multiple OR procedures and general anesthesia exposures if the second ear becomes affected. Since this study procedure is conducted in-office, it is proposed that the decision to perform unilateral or bilateral TT placement for AOM with effusion be based on subject preference and physician clinical judgment regarding the likelihood of disease developing in the opposite ear, similar to the Guideline recommendation for chronic OME.

The indications for tube placement have been clarified (as noted in italics) in instances where unilateral placement may be deemed appropriate by the physician and acceptable by the subject. The clinical indications for tube placement for children include:

- Bilateral TT insertion for bilateral otitis media with effusion (OME) for 3 months or longer (chronic OME) and documented hearing difficulties;
- *Unilateral or bilateral* TT insertion for unilateral or bilateral OME*, respectively,* for 3 months or longer (chronic OME) and symptoms that are likely attributable to OME that include, but are not limited to, vestibular problems, poor school performance, behavioral problems, ear discomfort, or reduced quality of life;
- *Unilateral or bilateral* TT insertion for recurrent acute otitis media (AOM) with unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy, where recurrent AOM is defined as three or more AOM episodes in the past 6 months or at least 4 AOM episodes in the past 12 months with at least 1 in the past 6 months.

In this study, the subject will be informed of the risk of subsequent OME or AOM in the contralateral ear and the potential need for a second tube insertion procedure should this occur. Prior to procedure, the Investigator must document which ears are intended for in-office tube placement.

12.2.2. Concomitant Medications

All prior and concomitant medications will be recorded. Prior medications will include all prescription and over-the-counter medications taken up to 28 days before procedure. All concomitant medications, and changes to medications, will be recorded during each subject's study enrollment period. Medications may be prescribed based on Investigator's discretion, except for drugs or devices under investigation through a different protocol.

12.2.3. Cranial Nerve Physical Exam

A standard cranial nerve physical exam will be employed at screening, post-procedure and at the follow-up visit to identify any potential adverse effects. [redacted] Any abnormalities will be recorded at screening and at the follow-up visit and the subject will be assessed for any adverse events. [redacted]

12.2.4. Otoscopy

An otoscopic exam will be conducted for both ears in all subjects for all study visits. The otoscopic examination will be used to visually examine the condition of the external ear canal and TM. Routine ear cleaning may be conducted only to the extent necessary to ensure the tympanic membrane and ear canal are free from matter that may interfere with iontophoretic delivery and to ensure visualization of the tympanic membrane.

The exam will be used to confirm eligibility and to assess the ear canal and TM for changes or adverse effects. Presence or absence of middle ear effusion will be assessed. In addition,

appearance of the myringotomy wound and patency of the tympanostomy tube (Group B only) will be evaluated at the follow-up visit. Tube functional patency will be determined through clinical assessments including otoscopic examination and tympanometry.

The screening otoscopic exam may be conducted up to 28 days prior to procedure and will be conducted for both ears of all subjects to determine eligibility and ears selected (Group A) or indicated (Group B) for treatment. Otoscopic examination is considered standard of care for the Group B patient population and may be obtained prior to study informed consent as a screening assessment within 28 days prior to procedure. Otoscopic images may be collected prior to and following iontophoresis.

12.2.5. Tympanometry

Standard tympanometry for both ears will be employed to assess TM function at screening (within 28 days prior to procedure) and at the follow-up visit for all subjects. Tympanometry data recorded will include tympanogram type, ear canal volume, peak pressure and static acoustic immittance and gradient as an objective measure of tube patency and middle ear status. If adequate tympanometer seal or a valid tympanogram cannot be achieved for screening tympanometry evaluation (eligible ears for Group A subjects and indicated ears for Group B subjects), the subject will be considered a screening failure, and will not be eligible for the study. Tympanometry is considered standard of care for the Group B patient population and may be obtained prior to study informed consent as a screening assessment within 28 days prior to procedure. Tympanostomy tube functional patency will be determined through clinical assessments including otoscopic examination and tympanometry.

12.2.6. Audiometry

Audiometry will be employed to evaluate hearing status and TM function for both ears at screening (within 28 days prior to procedure) and at the post-procedure follow-up visit for all subjects. Threshold testing will be conducted for each ear using air conduction and bone conduction at a minimum of 500, 1000, 2000 and 4000 Hz.

Audiometry is considered standard of care for the Group B patient population and may be obtained prior to study informed consent as a screening assessment within 28 days prior to procedure.

12.2.7. Anesthesia Effectiveness

Following iontophoresis for Group A, the Investigator will gently tap the TM once with a standardized dull otologic instrument. The tap will occur on the anterior half of the TM at the location where the tympanostomy tube would theoretically be placed. The Investigator will assess whether the TM is adequately anesthetized for a hypothetical tympanostomy tube placement based on subject response to the TM tap which is recorded via VAS. [redacted]

For Group B, the Investigator will inspect the ear canal and TM following iontophoresis. and then lightly tap on the anterior half of the TM at the location where the tympanostomy

tube will be placed to elicit subject sensation which is recorded via VAS for each ear. [redacted] The Investigator will assess whether the TM is adequately anesthetized for the tympanostomy tube placement based on subject response to the TM tap for each ear. This tap assessment method has been used successfully in prior studies to determine adequate anesthesia for subsequent tympanostomy tube placement for both children and adults.

12.2.8. Tolerability (VAS)

The Visual Analogue Scale (Figure 9) is an instrument for assessing procedural pain consisting of a 10cm line, where the ends of the line represent the extreme limits of pain intensity ("No pain" to "Worst possible pain").[42] The subject reports their pain intensity by making a mark along the line and the line is measured to convert the subject response to numeric score (0-10 in centimeters). The VAS is validated for use in subjects 8 years of age and older.[35] A standardized script will be read to the subject to ensure consistent interpretation of the pain rating task. [redacted]

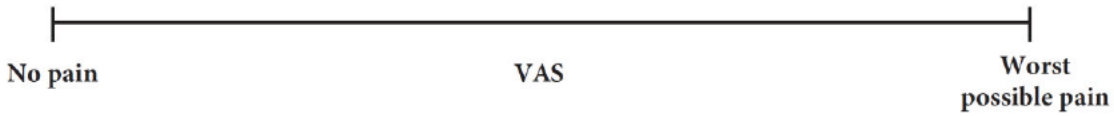


Figure 9. Visual Analogue Scale (not shown to scale)

[redacted]

[redacted]

12.2.10. Vital Signs (Group B)

Vital signs (diastolic and systolic blood pressure, heart rate, respiratory rate and pulse oximetry) measurements will used to evaluate baseline and peri-procedural vital signs to assess for any systemic effects of administered drug. Vital signs measurements will be recorded 15 minutes and immediately prior to iontophoresis, immediately following iontophoresis, following tube placement and at 30 and 60 minutes after completion of iontophoresis. Subjects who experience significant changes in vital signs (30% or greater compared to baseline) will undergo continued vital sign assessment until the vital sign measurements have returned to baseline (ie, beyond the 1-hour post-procedure evaluation period). Additionally, significant changes (30% or greater compared to baseline) will be considered adverse events.

12.3. Subject Recruitment and Informed Consent

For Group B recruitment, consecutive potentially-eligible patients presenting to the study site will be offered the opportunity to participate in the study by the investigator. For both Groups A and B, subject recruitment will occur through the use of Sponsor and IRB-approved advertisements and information sheets.

The basic objective of the study, the potential benefits and risks of participating, use and protection of their personal information, and the option to not participate will be fully explained to all prospective subjects as specified in and in compliance with 21CFR§50, the Declaration of Helsinki, and according to the principles of ISO14155. The Investigator or delegated clinical site research staff will answer all questions to the subject's satisfaction and will allow ample time for the subject to read the informed consent form and have additional questions answered. Subjects will be informed that the trial will be registered in the clinical trial registry databank maintained by the National Institutes of Health/National Library of Medicine (NIH/NLM). All potential subjects will be informed through both verbal and written information, and will sign an informed consent, according to local requirements, which states that any withdrawal from the study will neither prejudice nor in any way affect their future treatment. Subject consent will be obtained in writing prior to any study-related subject data collection or procedures being performed on the subject. A copy of the completed informed consent form will be given to the subject and the original will be placed in the Investigator's study record.

If new information that may affect a subject's willingness to participate or continue in the study, the Sponsor will notify the IRB and modify the informed consent form as appropriate.

All individuals that sign the informed consent will be considered enrolled subjects.

[redacted]

[redacted]

12.4. Screening Evaluations

After written informed consent is obtained, the subject is considered enrolled in the study and will be screened for inclusion and exclusion criteria.

Screening evaluations may be conducted on day of procedure or at a separate visit up to 28 days prior to procedure. The Screening Evaluations include (in any order):

1. Medical history and concomitant/prior medications
2. Cranial nerve physical exam
3. Microscopic otoscopy with optional ear cleaning
4. Tympanometry and Audiometry (in either order)
5. Inclusion/Exclusion

12.5. Procedure

12.5.1. Vital Signs (Group B)

Vital signs (diastolic and systolic blood pressure, heart rate, respiratory rate and pulse oximetry) will be monitored 15 minutes and immediately prior to iontophoresis, and again immediately following iontophoresis, following tube placement, 30 minutes and 60 minutes after completion of iontophoresis for all Group B subjects.

12.5.2. Otoscopic Examination and Ear Preparation

An otoscopic exam will be conducted using a microscope for all ears planned for treatment for subjects in Groups A and B prior to procedure. The otoscopic examination will be used to visually examine the condition of the external ear canal and TM. Routine ear cleaning may be conducted, if needed, only to the extent necessary to ensure the tympanic membrane and ear canal are free from matter that may interfere with or influence the evaluation and to ensure visualization of the tympanic membrane. Changes in concomitant medications will be recorded.

12.5.3. Earset Sizing

The IPS Earset is available in 6 sizes. The ear sizing procedure will be performed according to the Instructions for Use (IFU) provided with the IPS. If the subject's ear is not compatible

with the ear plug and fit cannot be established to ensure the earplug can properly seal in the ear canal, the subject will be considered a screening failure.

12.5.4. Anesthetic Solution Preparation

Ten (10) mL of 2% lidocaine/1:100,000 epinephrine anesthetic solution will be warmed to body temperature prior to instillation in the ear canal to minimize the caloric effect.

12.5.5. Earset Placement and Drug Instillation

Baseline tolerability will be assessed before placement of the Earset. The Earset ear plug of the size determined in the ear sizing procedure is then placed into the ear canal. Once the ear plug is positioned, the protective liner is removed, exposing the PSA to the ear canal. Circumferential pressure is applied through the ear plug against the surface of the ear canal, ensuring adhesion of the PSA. The Earset's integrated fill system is used to instill the selected drug into the ear canal. This process is repeated for the second ear, as applicable.

The Electrode Cable is snapped to the Return Electrode Patch. The Return Electrode Patch is then attached to the patient at a clean, dry site (such as the shoulder near the base of the neck) that is clear of lesions, bony protuberances and excessive hair. Prior to placing the return electrode on the patient, the investigator will assess the location for pre-existing erythema using the five point Draize erythema score where 0 indicates no erythema, 1 = very slight erythema (barely perceptible), 2 = well-defined erythema, 3= moderate to severe erythema, 4= severe erythema to slight eschar formation.[43] The location will be assessed again following iontophoresis.

12.5.6. Start of Iontophoresis

To begin anesthesia, the applicable Control Unit button(s) are pressed to initiate current. Initiation of current represents the beginning of the iontophoresis procedure. There are two buttons, one for each ear. Without interruptions, the Control Unit operation will take approximately 10 minutes. Progress through the iontophoresis cycle can be monitored via the status bars on the Control Unit which fill to indicate progress toward completion.

The procedure can be paused at any time, and then resumed. The Control Unit will account for these pauses to ensure consistent current dose delivery, and will provide a visible and audible signal when complete.

For Group A subjects randomized to sham iontophoresis, all procedures will take place as described above. The iontophoresis unit will not be activated, as dictated by the randomization schedule. [redacted]

[redacted]

12.5.7. Anesthetic Solution and Return Electrode Patch Removal

At the end of iontophoresis, the Earset(s), and Return Electrode Patch are removed and the anesthetic solution is removed from the ear canal either by wick or head tilting.

The return electrode location will be assessed by the treating physician upon completion of iontophoresis and removal of the return electrode patch. Observations will be graded using the five point Draize erythema score where 0 indicates no erythema, 1 = very slight erythema (barely perceptible), 2 = well-defined erythema, 3= moderate to severe erythema, 4= severe erythema to slight eschar formation.[44] Scores of 3 or greater will be considered adverse events.

12.5.8. Post-Iontophoresis Anesthesia Effectiveness (Group A)

Following iontophoresis, the Investigator will inspect the ear canal and TM using the microscope. The Investigator will then lightly tap on the anterior half of the TM to elicit subject sensation (at the location where a tympanostomy tube would theoretically be placed) which is recorded via VAS. [redacted]

If an unexpected serious complication occurs during the procedure, the procedure will be terminated. The Investigator will take all appropriate intra- and post-treatment measures to ensure subject safety and proper treatment. The Investigator will notify Tusker Medical and their IRB immediately, but in no instances greater than 24 hours of the incident.

12.5.9. Post-Iontophoresis Anesthesia Effectiveness (Group B)

Following iontophoresis, the Investigator will inspect the ear canal and TM using the microscope. The Investigator will then lightly tap on the anterior half of the TM at the location where the tympanostomy tube will be placed to elicit subject sensation which is recorded via VAS for each ear. [redacted] The Investigator will assess whether the TM is adequately anesthetized for the tympanostomy tube placement based on subject response to the TM tap for each ear. This tap assessment method has been used successfully in prior studies to determine adequate anesthesia for subsequent tympanostomy tube placement for both children and adults.

12.5.10. Tympanostomy Tube Placement (Group B only)

In at least one ear, the Investigator will place the TT using the TDS while the subject's head is gently stabilized by the clinic staff, as is typical for standard of care ear examinations. If the TT is not successfully placed by the TDS device, the investigator may choose to attempt tube placement with another TDS device. [redacted]

Following TDS tube placement, the subject will report their post-tube placement ear discomfort for each ear undergoing tube placement using the VAS. For bilateral tube placement subjects, the 'worst' ear pain score (highest score) will be used for analysis of the tube placement tolerability primary endpoint. [redacted]

[redacted] The subject's VAS score for each ear following suction will be recorded. Post-operative care, including otic drops, will be prescribed per investigator's discretion. All post-operative medications will be documented.

If an unexpected serious complication occurs during the procedure, the procedure will be terminated. The Investigator will take all appropriate intra- and post-treatment measures to ensure subject safety and proper treatment. The Investigator will notify Tusker Medical and their IRB immediately, but in no instances greater than 24 hours of the incident.

12.5.11. Cranial Nerve Exam

The cranial nerve physical exam will be conducted post-procedure.

12.6. Group A Follow-up

Follow-Up Visit at 3 Days Post-Procedure (-1/+2 Days)

1. All subjects are required to return for the 3-day post-procedure follow-up visit.

2. A microscopic otoscopic examination will be used to visually examine the condition of the external ear canal and TM. If any adverse otoscopic findings are observed, microscopic images will be collected for each ear.

3. The subject will complete audiometry and tympanometry, and cranial nerve physical exam.

4. The ears will be evaluated for any adverse events.

5. If there are suspected procedure, device or drug-related adverse findings, the subject is required to return for follow-up at 12 ± 3 days post-procedure.

6. If there are no unresolved suspected procedure, device or drug-related adverse findings, the subject will then be exited from the study.

7. Follow-up for other adverse events will be determined according to Investigator discretion.

Follow-Up Visit at 12 Days Post-Procedure (±3 Days)

1. Only subjects with suspected procedure, device or drug-related adverse events that are not resolved at the 3-day visit, or per Investigator decision, are required to complete the 12 days post-procedure follow-up visit.

2. A microscopic otoscopic examination will be used to visually examine the condition of the external ear canal and TM. If any adverse otoscopic findings are observed, microscopic otoscopic images will be collected for each ear.

3. The ears will be evaluated for any new or ongoing adverse events.

4. The subject will complete audiometry and tympanometry, and cranial nerve physical exam.

5. The subject will then be exited from the study.

12.7. Group B Follow-up

3-Week Post-Procedure Follow-Up Visit (+/- 7 Days)

1. All subjects are required to return for the 3-week post-procedure follow-up visit.

2. An otoscopic examination will be used to visually examine the condition of the external ear canal, TM, myringotomy wound and tube patency.

3. The subject will complete audiometry and tympanometry, and cranial nerve physical exam.

4. Subjects will be evaluated for any adverse events, and changes in concomitant medications will be recorded.

5. The subject will then be exited from the study

12.8. Summary- Study Evaluations, Group A

The schedule of evaluations for each study visit for Group A is presented in **Table 2**.

Table 2. Schedule of Evaluations – Group A

Evaluation	Screening	Procedure	3 Days (-1 /+2 days)	12 Days * (±3 days)
Informed Consent	✓			
Medical History	✓			
Cranial Nerve Physical Exam	✓	✓	✓	✓
Inclusion/ Exclusion Criteria	✓	✓ (verification)		
Concomitant Medications	✓	✓	✓	✓
Otoscopy	✓	✓	✓	✓
Tympanometry	✓ (within 28 days prior to Procedure)		✓	✓
Audiometry	✓ (within 28 days prior to Procedure)		✓	✓
Randomization	✓			
Iontophoresis/Sham Iontophoresis		✓		
Anesthesia Effectiveness		✓		
Adverse Events		✓	✓	✓
Study Exit			✓ (if no 12 day visit required)	✓

12.9. Summary – Study Evaluations, Group B

The schedule of evaluations for each study visit for Group B is presented in **Table 3**.

Table 3. Schedule of Evaluations – Group B

Evaluation	Screening	Procedure	3 Weeks (-/+ 7 days)
Informed Consent	✓		
Medical History	✓		
Cranial Nerve Physical Exam	✓	✓	✓
Concomitant Medications	✓	✓	✓
Inclusion/ Exclusion Criteria	✓	✓ (verification)	
Otoscopy	✓ (*within 28 days prior to Procedure)	✓	✓
Tympanometry	✓ (*within 28 days prior to Procedure)		✓
Audiometry	✓ (*within 28 days prior to Procedure)		✓
Procedure		✓	
Vitals		✓	
Anesthesia Effectiveness		✓	
Tube Placement Tolerability		✓	
Optional Suction, Suction Tolerability		✓	
Adverse Events		✓	✓
Study Exit			✓

*Otoscopic examination, tympanometry and audiometry are considered standard of care for this patient population. Data obtained from these assessments within 28 days prior to procedure may be included as screening assessments.

13.0 ASSESSMENT OF SAFETY

13.1. Adverse Events

All reported or observed adverse events that occur during or after the procedure will be recorded. The study Investigator will determine whether an adverse event has occurred, whether life-threatening, serious or non-serious. Pre-existing conditions should not be reported as adverse events unless there has been a worsening in the severity or frequency,

which cannot be attributed to natural history or progression of the disease. This definition does not depend on the causal relationship with the device, drug or protocol requirements.

Any change of clinical significance, including vertigo, nausea and vomiting, derived from the protocol evaluations including observations and patient-reported findings will be included as adverse events. Changes in vital signs 30% or greater compared to baseline will be considered adverse events.

All Adverse Events (AEs) will be recorded on dedicated AE case report forms. The event, date of onset, severity, seriousness, duration, treatment, outcome, date or resolution and relationship to device, procedure or drug will be recorded on the AE case report form (CRF). AEs will be categorized by seriousness, relatedness to procedure, investigational drug, or device whether anticipated or unanticipated. All adverse events will be coded using standard terms.

13.2. Serious Adverse Events

If an unexpected serious complication resulting in an adverse event occurs during the procedure, the procedure will be terminated. The Investigator will take all appropriate intra- and post-procedural measures to ensure subject safety and proper treatment. In the event of a serious adverse event at any time during the study, the Investigator will notify the Sponsor and their IRB immediately or no later than within 24 hours.

All Serious Adverse Events that have not resolved by the end of the subject's participation in the study must be followed until the event resolves, improves, or stabilizes. The investigator should report any follow-up information as it becomes available.

13.3. Adverse Event Definitions

Adverse Event (AE)
An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the procedure or use of the device or investigational drug, and does not imply judgment about causality.

Serious Adverse Event (SAE)
AEs are classified as serious or non-serious. A serious adverse event is any AE that is:

- Fatal
- Life-threatening
- Requires or prolongs hospital stay
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Led to fetal distress, fetal death or congenital abnormality or birth defect

- An important medical event that may jeopardize the subject, and may require medical or surgical intervention to prevent one of the other serious outcomes noted above.

Life Threatening Adverse Event or Life-Threatening Suspected Adverse Reaction
An adverse event or suspected adverse reaction is considered life threatening if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

Unanticipated Adverse Device Effect (UADE)
A UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

In order to ensure subject safety during the study, all adverse events assessed as "serious" in the opinion of the Investigator will be reviewed by the Medical Monitor to determine any causal relationship to the study drug, device or procedure. All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events. Non-serious adverse events must still be documented on the appropriate CRF.

Reporting
The sponsor will notify FDA, all reviewing IRBs and all participating Investigators of potential serious risks, from this study or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting, including:

1. Suspected adverse drug reactions that are considered both serious and unexpected,

2. Findings from other studies that suggest a significant risk in humans exposed to the drug,

3. Findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug, and

4. An increased rate of occurrence of serious suspected adverse reactions.

In addition, the sponsor will notify FDA, all reviewing IRBs and participating investigators within 10 working days after the Sponsor first receives notice of an Unanticipated Adverse Device Effect.

13.4. Adverse Event Classification

Adverse Event Severity
All adverse events will be classified as to the severity of the event based on the definitions consistent with AE severity grading scale provided by the National Cancer Institute, of the NIH and US Department of Health and Human Services – Common Terminology Criteria

for Adverse Events v.4.03 (CTCAE) June 14, 2010 (**Table 4**).[45] Grade level of adverse event refers to the severity of the event.

Table 4. Table of Adverse Event Severity

AE Severity	Definition
Grade 1 – Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 – Moderate	Minimal, local or non-invasive intervention indicated; limiting normal daily activities
Grade 3 – Severe	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling limiting self-care
Grade 4 – Life Threatening	Life threatening consequences; urgent intervention indicated
Grade 5 – Death	Death related to adverse event

Any increase in the severity of an AE should be documented.

Adverse Event Causality

Causality regarding device, drug and/or procedure relationship will be assigned by the Investigator to all adverse events according to the definitions provided in **Table 5**.

Table 5. Table of Adverse Event Causality

Causality	Description*
Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to procedure, device or drug administration/exposure, which cannot be explained by concurrent disease, other interventions or other drugs and considered definitely related to the study drug, device or procedure.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to procedure, device or drug administration/exposure, unlikely to be attributed to concurrent disease, other interventions or drugs.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to procedure, device or drug administration/exposure, but which could also be explained by concurrent disease, other interventions or drugs.
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to procedure, device or drug administration/exposure which makes a causal relationship improbable, and in which concurrent disease, other interventions, other drugs or chemicals provide plausible explanations. A *Not Related* event may also not have a reasonable temporal relationship to procedure, device or drug administration/exposure.

*Causality definitions derived from WHO-UMC Causality Assessment Scale[46]

Adverse Event Criteria – Hearing Loss

Audiometry will be used to assess changes to hearing thresholds for all ears. Investigators will diagnose post-treatment hearing impairment/loss if audiometry indicates a greater than 15-decibel (dB) change (worsening) in air conduction pure tone average for either ear. Classification of the level of hearing loss/impairment will be according to the American Academy of Audiology Childhood Screening Guidelines, as outlined in **Table 6**.[47,48]

Table 6. Table of Hearing Threshold Change (Worsening) Classification

Level	Threshold Change
Slight	16-25 dB
Mild	26-40 dB
Moderate	41-55 dB
Moderately Severe	56-70 dB
Severe	71-90 dB
Profound	91 dB or greater

13.5. Safety Monitoring

Investigators will report all serious adverse events to the Sponsor within 24 hours of identification. The Sponsor and Medical Monitor will promptly review information relevant to the safety of the device or drug. All serious and all unanticipated adverse events, as well as all adverse events related to the ear, will be reviewed within 24 hours of Tusker Medical awareness. The Investigator is responsible for reporting events to the IRB according to IRB requirements, and the Sponsor is responsible for reporting to regulatory authorities according to regulatory requirements.

If the Sponsor determines that study participation poses a significant risk to subjects, the sponsor shall suspend or discontinue the study and notify regulatory authorities, investigators and IRBs as appropriate.

Adverse Events will be adjudicated as deemed appropriate by the Medical Monitor. The Medical Monitor will review all AEs and their coding for accuracy and consistency periodically.

13.6. Device Malfunctions

Any inadequacy of the device or packaging with respect to its identity or performance will be recorded as a device malfunction. Information regarding the device identity (eg, device name/code and lot number), temporal aspect of the malfunction (eg, prior to opening,

during preparation during procedure), nature of the malfunction and relatedness to potential adverse events will be collected on appropriate CRFs.

[redacted]

14.0 STATISTICAL METHODS

This study will consist of two independent Groups, referred to as 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 will consist of 40 healthy adult subjects aged 18-50, enrolled at two investigational centers in the US. Group A subjects will be randomized to receive unilateral (1 ear) active lidocaine iontophoresis or unilateral 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 both ears). After the completion of the iontophoresis, the tympanic membrane will be tapped with a dull otologic probe to test anesthesia effectiveness. The subject will rate the level of pain using the VAS after the ear is tapped.

Group B will consist of 30 adults age 18 years or older 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 tube insertion using the TDS in all ears that require tube insertion. The subject will rate the pain on tube insertion using the VAS, and the pain score will be compared to a fixed performance goal.

14.1. 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.

14.2. General Statistical Methods

Descriptive statistics will be provided. Data collected in the study will be summarized overall and as defined in the protocol.

Routine presentation of continuous variables in descriptive tables will include mean, standard deviation, sample size, and median. Categorical or binary variables will be presented with numerator, denominator, and percent.

The SAS system (v9.2 or later) or R will be used to perform all statistical analyses.

14.3. Group A – Statistical Methods

14.3.1. Randomization & Blinding

Subjects will be randomized (1:1) to either active lidocaine iontophoresis or sham lidocaine 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]

[redacted]

[redacted]

14.3.2. Analysis Sets

14.3.2.1. 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. Only subjects who do not complete the procedure due to reasons not related to iontophoresis discomfort (eg, anatomy not compatible with device fit) will be excluded. Subjects will be analyzed as randomized.

14.3.2.2. Per Protocol Set

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).

14.3.2.3. Safety Analysis Set

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

14.3.3. Primary Endpoint Analysis

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

The null and alternative hypotheses are:

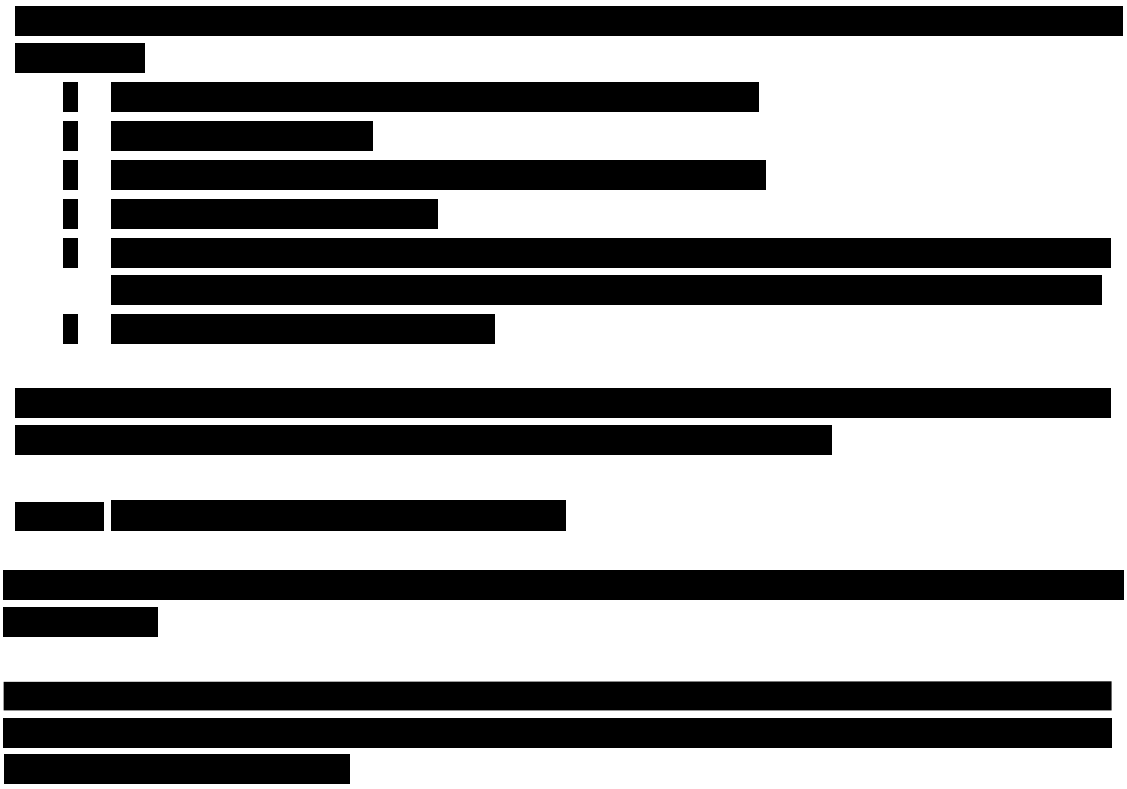
$$H_o : \mu_T - \mu_S = 0$$
$$\text{vs.}$$
$$H_1 : \mu_T - \mu_S < 0$$

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.

14.3.4. Safety Analysis

All reported or observed adverse events that occur for subjects in the Safety Analysis Set during or after the procedure will be recorded. All AEs will be tabulated by treatment group. AEs will be summarized by preferred terms and system organ class using the Medical Dictionary for Regulatory Activities (MedRA). The frequency of each event will be summarized by seriousness, severity and by relationship to the study device, procedure and/or drug. Separate summaries will be provided for SAEs and AEs related to study device, procedure and/or drug. In the event a subject reports the same event several times (eg, otalgia), the first occurrence of the worst reported case of the event will be used for the purpose of analysis.



14.4. Group B – Statistical Methods

14.4.1. Analysis Sets

14.4.1.1. Full Analysis Set (FAS)

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

14.4.1.2. 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).

14.4.1.3. Safety Analysis Set

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

14.4.2. Primary Endpoint Analysis

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. The primary analysis for Group B will be performed based on completers in the Per Protocol set, specifically including only subjects with VAS scores following successful tube insertion for all ears indicated for treatment (both ears for bilateral subjects and one ear for unilateral subjects). [redacted]

14.4.3. Safety Analysis

All reported or observed adverse events that occur for subjects in the Safety Analysis Set during or after the procedure will be recorded. All AEs will be tabulated. AEs will be summarized by preferred terms and system organ class using the Medical Dictionary for Regulatory Activities (MedRA). The frequency of each event will be summarized by seriousness, severity and by relationship to the study device, procedure and/or drug. Separate summaries will be provided for SAEs and AEs related to study device, procedure and/or drug. In the event a subject reports the same event several times (eg, otalgia), the first occurrence of the worst reported case of the event will be used for the purpose of analysis.

[redacted]

[redacted]

[redacted]

14.6. Handling Drop Outs or Missing Data

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 the sensitivity analyses only, and will not be included in the primary analysis. Only subjects with scores after tubes are successfully placed in all indicated ears (one tube if indicated for unilateral treatment and two tubes if indicated for bilateral treatment) will be included in the primary analysis. [redacted] Reasons for discontinuation will be documented and presented in the clinical study report.

[redacted]

14.7. 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.

15.0 ETHICS/PROTECTION OF HUMAN SUBJECTS

Prior to enrolling subjects, all sites must have the approval of an Institutional Review Board (IRB) responsible for reviewing clinical studies at the study site. The IRB must also approve the subject Informed Consent as well as recruiting advertisements and subject-facing information. Amendments to any of these documents must also be approved by the IRB. No subjects will be consented or enrolled to a site until IRB approval has been received in writing. The Informed Consent process is described in **Section 12.3.**

15.1. Subject Confidentiality

Subject confidentiality will be maintained at all times during the study. A unique subject identifier will consist of (1) a Protocol Identifier, (2) an Investigational Site identifier, and (3) a consecutive subject number with designated group assignment (A or B).

Example: 7003-JON-A01 in Group A

7003 = 4 digit Protocol Number

JON = Investigator Dr. Jones

A01 = Number of subject enrolled

The Investigator or evaluation personnel at each study site will assign the subject identifier and access to this identifier will be restricted to the Investigator and evaluation personnel. The key to the subject identifier and subject data collection sheets containing the subject's name and identification code will be securely maintained at each study site.

16.0 PREMATURE TERMINATION OR WITHDRAWAL

16.1. Subject Stopping Criteria

Subjects who do not complete the study procedure will be encouraged to remain in the study to complete post-procedure evaluations. If a subject withdraws prematurely from the study, a genuine effort must be made to determine the reason(s) why the subject failed to return for the procedure or follow-up visit or discontinued the study, and the reason must be recorded on the appropriate CRF.

Potential reasons for discontinuation include:

- Subject decides it is in their best interest to withdraw
- Subject expresses intolerable discomfort during the procedure and indicates they wish to stop the procedure and withdraw

- Serious adverse event that requires withdrawal from the study
- Investigator decides it is in the subject's best interest to be withdrawn if subject is experiencing intolerance or intolerable reaction to the procedure.

If the subject wishes to discontinue participation in the study, the Investigator will attempt to have the subject continue participation to complete follow-up assessments unless the subject's safety is compromised. All Serious Adverse Events that have not resolved by the end of the subject's participation in the study, must be followed until the event resolves, stabilizes or becomes non-serious.

All potential subjects in the study will be verbally informed and will sign an informed consent in compliance with 21CFR §50 that states that any withdrawal from the study will neither prejudice nor in any way affect their future treatment.

Prior to designating a subject as lost to follow-up, the site must provide documented evidence of three (3) good faith attempts to contact the subject to which there has been no response. At that point the subject will be considered lost-to-follow-up and withdrawn from the study.

[redacted]

[redacted]

17.0 INVESTIGATOR RESPONSIBILITIES

Investigators who participate in this study will conduct the study according to the protocol, the Declaration of Helsinki, GCP and applicable regulatory requirements. Tusker Medical will sponsor the conduct of the study at up to 8 investigational centers. This study will be performed under the direction and responsibility of the physician investigator at each study site. It is the responsibility of the Investigators to ensure study material is reviewed and approved by all applicable Institutional Review Boards (IRB), hospital committees, and administrative personnel as required.

The Investigator is responsible for the execution of the study, proper performance of participating personnel, ensuring adherence to the protocol and schedule of procedures, and for the control of devices under investigation. The Investigator is also responsible for protecting the rights, safety, and welfare of subjects under the investigator's care, and ensuring that written informed consent is obtained.

The Investigator is responsible for data confidentiality, quality, and completeness, and proper data storage in a secure file for a period of time as indicated in the protocol, Clinical Trial Agreement (CTA) and if mandated, by the respective IRBs.

The Investigator and site personnel directly involved with the study will receive training in the protocol and use of devices prior to initiation of the study. This training will be conducted by the Sponsor (Tusker Medical, Inc.) or designee, prior to initiation of the study.

18.0 SPONSOR

Tusker Medical, Inc. is the device manufacturer as well as the study sponsor ("Sponsor"). The Sponsor will work with the study site under the terms of the Clinical Trial Agreement (CTA).

The Sponsor contact is as follows:

Tusker Medical, Inc.
155 Jefferson Drive, Suite 200
Menlo Park, CA 94025

[redacted]

[redacted]

19.0 MONITORING

Tusker Medical, Inc. (Sponsor) or designee will monitor the study sites to ensure investigators are in compliance with the protocol; subject informed consent forms are properly completed; adequate protection of the rights of the human subjects and the quality and integrity of the resulting data; study data is verified against source documents for key safety and effectiveness variables; investigational devices and drug are properly controlled; and verification that reports are filed in accordance with the protocol and the appropriate regulations. Monitoring will be conducted according to the Sponsor's monitoring procedure and study monitoring plan.

20.0 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

Access to investigational drug and devices shall be controlled and the investigational drug and devices shall be used only in the clinical investigation and according to the protocol. The Sponsor shall keep records to document the physical location of all investigational drug and devices from shipment to the investigation sites until return or disposal. Drug and devices will be stored according to product labeling. The principal investigator or an authorized designee shall keep records documenting the receipt, use, return, and disposal of the investigational drug and devices, which shall include (a) the date of receipt, (b) identification of each investigational drug and device (batch number/serial number or unique code), (c) the expiration date, (d) the date or dates of use, (e) subject identification, and (f) the date of return of unused, expired or malfunctioning investigational products, if applicable.

21.0 DEVIATIONS

A protocol deviation is defined as any event where the Investigator or site personnel deviate from the study protocol or study procedures for any reason. It is the Investigator's responsibility to ensure that there are no protocol deviations throughout the life of the study. In the event that a non-emergency protocol deviation is identified, at the time of identification, the personnel identifying the event will review and define appropriate

corrective actions to prevent recurrence. The IRB will be notified as applicable. Any deviations from this protocol will be documented by the site on a protocol deviation CRF.

22.0 DATA HANDLING AND RECORD KEEPING

22.1. Source Data and Case Report Forms

All study data will be captured on source documents by the Investigational Site. Data from the source documents will be recorded to CRFs by site personnel that have been trained on the protocol and CRF completion.

22.2. Data Quality Assurance

Accuracy and reliability of the clinical study data will be ensured by selection of qualified investigators, and appropriate study centers, review of protocol procedures with the investigators and associated personnel prior to the study, and by periodic monitoring visits by the sponsor. CRFs will be reviewed for accuracy and completeness by the sponsor during on site monitoring visits and after their return to the sponsor, and any discrepancies will be resolved with the investigator or designees, as appropriate.

22.3. Record Retention

All clinical sites will maintain all records pertaining to this study for a minimum of two years after marketing approval or formal discontinuation of investigational product development. The Sponsor will notify the clinical sites of the date of discontinuation. No study-related records, written or electronic, will be destroyed or transferred without specific written approval by the Sponsor.

23.0 PUBLICATION POLICY

The CTA mutually signed by the Investigator(s) and Tusker Medical, Inc., defines and describes the nature of the study agreement.

The Sponsor retains the rights to this protocol and the CRFs before and after data entry. Tusker Medical, Inc. reserves the right to review any reports of this study to verify that the information is accurate and to ensure the content and timing of any such publication is mutually agreed upon by the Investigator(s) and Tusker Medical, Inc. Draft abstracts, manuscripts, and materials for presentation at scientific meetings should be provided to the sponsor at least 30 working days prior to submission.

Clinical trial information will be registered in the clinical trial registry databank maintained by the National Institutes of Health/National Library of Medicine (NIH/NLM) per FDAAA 801 requirements. If a future publication results from this study, authorship will be established according to ICMJE guidelines.

24.0 REFERENCES

[1] Rosenfeld RM, Schwartz SR, Pynnonen MA, Tunkel DE, Hussey HM, Fichera JS, Grimes AM et al. Clinical practice guideline: tympanostomy tubes in children. Otolaryngol Head Neck Surg, 2013; 149(IS):S1-S35.
[2] AAO-HNS Clinical Indicators, 2010: https://www.societyformiddleeardisease.org/Content/ClinicalIndicators/Myringotomy-and-Tympanostomy-Tubes-CI.pdf. Accessed on 02 July 2016.
[3] Otitis Media (Ear Infection), NIDCD, July 2002. NIH Pub No. 97-4216. 7 Aug 2008 http://www.nidcd.nih.gov/health/hearing/ otitism.asp.
[4] Klein J, Pelton S. Epidemiology, pathogenesis, clinical manifestations, and complications of acute otitis media. Up to Date, October 2008, 7 Aug 2008.
[5] Tusker Medical analysis of Truven Commercial, Medicaid and Medicare databases.
[6] Litman RS. Basics of Pediatric Anesthesia. Philadelphia, PA, 2013.
[7] Dewhirst E, Fedel G, Raman V et al. Pain management following myringotomy and tube placement: Intranasal dexmedetomidine versus intranasal fentanyl. Int J Pediatr Otorhinolaryngol, 2014; 78(7):1090-1094.
[8] Montague ML, Lee MSW, Hussain SSM. Human error identification: an analysis of myringotomy and ventilation tube insertion. Arch Otolaryngol Head Neck Surg, 2004;130:1153-1157.
[9] Isaacson G. Six sigma tympanostomy tube insertion: achieving the highest safety levels during residency training. Otolaryngol Head Neck Surgery, 2008; 139:353-357.
[10] Kesser BW, Derebery MJ, Friedman RA. (2010) Surgery of ventilation and mucosal disease. In: Otologic Surgery. Brackmann DE, ed. Pages 73- 91 (Philadelphia, PA: Saunders, 2010).
[11] Freeman SRM, Iseli CE, Kerr MBA, Kong JHK, Gibson WPR. Phenol application for tympanic membrane anesthesia. Clin Otolaryngol, 2007; 33:152-199.
[12] EMLA drug label; http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=1240, accessed 03June2016.
[13] Jyvakorpi M. A comparison of topical EMLA cream with Bonain's solution for anesthesia of the tympanic membrane during tympanocentesis. Eur Arch Otorhinolaryngol, 1996; 253: 234-236.
[14] Todd N. What your colleagues think of tympanostomy tubes 28 years later. Laryngoscope, 1999; 109:1028-1032.
[15] Markowitz-Spence L, Brodsky L, Syed N, Stanievich J, Vold M. Anesthetic complications of tympanostomy tube placement in children. Arch Otolaryngol Head Neck Surg, 2006; 116: 809-812.
[16] Hoffmann KK, Thompson GK, Burke BL, Derkay CS. Anesthetic complications of tympanostomy tube placement in children. Arch Otolaryngol Head Neck Surg, 2002; 128: 1040-1043.
[17] Ing C, Dimaggio C, Whitehouse A et al. Long-term differences in language and cognitive function after childhood exposure to anesthesia. Pediatrics, 2012; 130: e476.
[18] Wilder RT, Flick RP, Sprung J et al. Early exposure to anesthesia and learning disabilities in a population- based birth cohort. Anesthesiology, 2009; 110: 796.

[19] FDA Drug Safety Communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women. 12/14/2006, http://www.fda.gov/Drugs/DrugSafety/ucm519616.htm.
[20] Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children, Predictors and outcomes. Arch Pediatr Adolesc Med, 1996; 150:1238-45.
[21] Kain ZN, Mayes LC, Caldwell-Andrews AA et al. Sleeping characteristics of children undergoing outpatient elective surgery. Anesthesiology, 2002; 97:1093-101.
[22] Cravero JP, Beach M, Dodge CP, Whalen K. Emergence characteristics of sevoflurane compared to halothane in pediatric patients undergoing bilateral pressure equalization tube insertion. J Clin Anesth, 2000; (12): 397-401.

[redacted]

[34] Jensen MP, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Handbook of Pain Assessment. Turk DC, Melzack R, eds. Pages 135-151. The Guilford Press, New York, 1992.
[35] Stinson JN, Kavanagh T, Yamada J, Gill N, Stevens B. Systematic review of the psychometric properties, interpretability and feasibility of self-report pain intensity measures for use in clinical trials in children and adolescents. Pain, 2006; 125:143-157.

[redacted]

[39] Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain, 2003; 4(7):407-414.
[40] Rosenfeld RM, Schwartz SR, Pynnonen MA, Tunkel DE, Hussey HM, Fichera JS, Grimes AM et al. Clinical practice guideline: tympanostomy tubes in children. Otolaryngol Head Neck Surg, 2013; 149(IS):S1-S35.
[41] AAO-HNS Clinical Indicators, 2010: https://www.societyformiddleeardisease.org/Content/ClinicalIndicators/Myringotomy-and-Tympanostomy-Tubes-CI.pdf. Accessed on 02 July 2016.
[42] http:www.amda.com/tools/library/whitepapers/hopsiceinltc/appendix-a.pdf. Accessed on 09 Feb 2017.
[43] Draize JH, Woodard G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J. Pharmacol. Exp. Therapeutics, 1944; 82: 377–390.
[44] Draize JH, Woodard G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J. Pharmacol. Exp. Therapeutics, 1944; 82: 377–390.
[45] US Department of Health and Human Services, NIH, National Cancer Institute, "Common Terminology Criteria for Adverse Events (CTCAE), NIH Publication No 09-5410, Version 4.03, June 14, 2010.
[46] The use of the WHO–UMC system for standardized case causality assessment. Accessed from: http://WHO-UMC.org/graphics/24734.pdf. accessed on 29 May 2016.
[47] Clark JG: Uses and abuses of hearing loss classification. ASHA, 1981; 23(7):493– 500.
[48] American Academy of Audiology Childhood Hearing Screening Guidelines, Sept 2011. Accessed from: http://www.cdc.gov/ncbddd/hearingloss/documents/AAA_Childhood%20Hearing%20Guidelines_2011.pdf. accessed on 29 May 2016.

[redacted]