A PROSPECTIVE, SINGLE-ARM, MULTICENTER STUDY TO EVALUATE EFFECTIVENESS AND SAFETY OF TYMPANOSTOMY TUBE PLACEMENT USING THE TULA IONTOPHORESIS AND TUBE DELIVERY SYSTEMS FOR CHILDREN IN AN OFFICE SETTING

(OTTER; in-**O**ffice **T**ympanostomy **T**ube placem**E**nt in child**R**en)

Study Products:

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

Study Phase: Pivotal

Protocol #: CPR007001
Revision: E

IDE Number: G170193
NCT Number: NCT03323736

SPONSOR:
Tusker Medical, Inc.
155 Jefferson Drive
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USA
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MEDICAL MONITORS:
[redacted]

[redacted]

This protocol contains confidential information for use by investigators participating in this study and should be maintained in a secure location. It should not be duplicated or made available for review by any unauthorized person or firm.

A PROSPECTIVE, SINGLE-ARM, MULTICENTER STUDY TO EVALUATE EFFECTIVENESS AND SAFETY OF TYMPANOSTOMY TUBE PLACEMENT USING THE TULA IONTOPHORESIS AND TUBE DELIVERY SYSTEMS FOR CHILDREN IN AN OFFICE SETTING (OTTER; in-**O**ffice **T**ympanostomy **T**ube placem**E**nt in child**R**en)

Protocol Number: CPR007001

Approved By:

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

TABLE OF CONTENTS

TABLE OF CONTENTS **3**

1.0 INVESTIGATORS 7
2.0 STATEMENT OF COMPLIANCE 7
3.0 INVESTIGATOR SIGNATURE PAGE 8
4.0 LIST OF ABBREVIATIONS 9
5.0 PROTOCOL SUMMARY 10
6.0 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE 16
6.1. CLINICAL AND TECHNOLOGY BACKGROUND 16
7.0 STUDY DEVICES 20
7.1. DEVICE DESCRIPTIONS 20
7.1.1. IONTOPHORESIS SYSTEM 20
7.1.2. IONTOPHORESIS BASIC OPERATING PRINCIPLES 25
7.1.3. TUBE DELIVERY SYSTEM (TDS) 26
[redacted] 28
[redacted] 28
9.0 TUSKER MEDICAL CLINICAL EXPERIENCE 29
10.0 STUDY DESIGN 30
10.1. STUDY OBJECTIVE 30
10.2. OVERALL STUDY DESIGN – PHASES AND ENROLLMENT 30
10.3. DESIGN OF THE PIVOTAL STUDY PHASE 31
[redacted] 33
10.3.1.1. PROCEDURAL SUCCESS 33
10.3.1.2. TUBE PLACEMENT TOLERABILITY 34
10.4. STUDY POPULATION 36
10.4.1. DEFINITION OF ENROLLMENT 36
10.4.2. STUDY COHORT DEFINITIONS 36
10.4.2.1. LEAD-IN OR COHORT 36
10.4.2.2. LEAD-IN OFFICE COHORT 36
10.4.2.3. PIVOTAL COHORT 36
10.5. PRIMARY ENDPOINTS 36
10.6. SAFETY ENDPOINT 38
10.7. SECONDARY EFFECTIVENESS ENDPOINTS 38
10.7.1. TUBE PATENCY 38
10.7.2. TUBE RETENTION 38
10.7.3. ANESTHESIA EFFECTIVENESS 39
[redacted] 39
[redacted] 39
[redacted] 39
[redacted] 39
[redacted] 39
[redacted] 40
[redacted] 40
[redacted] 40
[redacted] 40
[redacted] 41
[redacted] 41
[redacted] 41
[redacted] 41
10.9. INCLUSION CRITERIA 41
10.10. EXCLUSION CRITERIA 42

11.0 Study Procedures 43
11.1. Investigator Training 43
11.2. Lead-In Procedures 43
[redacted] 44
11.4. Evaluation Methods 44
11.4.1. Diagnosis 44
11.4.2. Concomitant Medications 45
11.4.3. Cranial Nerve Physical Exam 45
11.4.4. Otoscopy 45
11.4.5. Tympanometry 46
11.4.6. Audiometry 46
11.4.7. Anesthesia Effectiveness 46
11.4.8. Tolerability (FPS-R) 47
11.4.9. Tolerability (FLACC) 47
11.4.10. Parent/Guardian Survey 49
11.5. Subject Recruitment and Informed Consent 49
11.6. Screening Evaluations 50
11.7. Procedure 50
11.7.1. Otoscopic Examination and Ear Preparation 50
11.7.2. Earset Sizing 50
11.7.3. Anesthetic Solution Preparation 50
11.7.4. Earset Placement and Drug Instillation 50
11.7.5. Start of Iontophoresis 51
11.7.6. Anesthetic Solution and Return Electrode Patch Removal 52
11.7.7. Post-Iontophoresis Anesthesia Effectiveness 52
11.7.8. Tympanostomy Tube Placement 52
11.7.9. Post-Procedure Otoscopy and Cranial Nerve Exam 53
11.7.10. Unsuccessful Procedures 53
[redacted] 53
11.9. 3-Week Post-Procedure Follow-Up Visit (+/- 7 Days) 54
11.10. 6, 12, 18 and 24-Month Post-Procedure Follow-Up Visits (+/- 28 days) 54
11.11. Summary – Study Flow and Study Evaluations 54
12.0 Assessment of Safety 56
12.1. Adverse Events 56
12.2. Serious Adverse Events 57
12.3. Adverse Event Definitions 57
12.4. Adverse Event Classification 59
12.5. Safety Monitoring 63
[redacted] 63
12.6. Device Malfunctions 64
13.0 Statistical Methods 64
13.1. General Statistical Methods 65
13.2. Analysis Sets 65
13.2.1. Full Analysis Set 65
13.2.2. Per Protocol Set 65
13.2.3. Safety Analysis Set 65
13.3. Primary Endpoint Analysis 65
13.4. Secondary Efficacy Endpoint Analyses 67
13.4.1. Tube Patency 67
13.4.2. Tube Retention 68
13.4.3. Anesthesia Effectiveness 68
[redacted] 68
[redacted] 68
[redacted] 69
[redacted] 69
[redacted] 69
[redacted] 69

13.6. SAFETY ANALYSIS 70
[redacted] 70
[redacted] 70
[redacted] 70
[redacted] 70
[redacted] 71
[redacted] 71
[redacted] 71
[redacted] 71
[redacted] 71
[redacted] 71
[redacted] 72
[redacted] 72
[redacted] 72
[redacted] 72
13.8. HANDLING DROP OUTS OR MISSING DATA 72
[redacted] 72
[redacted] 73
[redacted] 73
14.0 ETHICS/PROTECTION OF HUMAN SUBJECTS 73
14.1. SUBJECT CONFIDENTIALITY 73
15.0 PREMATURE TERMINATION OR WITHDRAWAL 73
15.1. SUBJECT STOPPING CRITERIA 73
15.2. STUDY STOPPING CRITERIA 74
16.0 INVESTIGATOR RESPONSIBILITIES 75
17.0 SPONSOR 76
18.0 MONITORING 76
19.0 INVESTIGATIONAL PRODUCT ACCOUNTABILITY 76
20.0 DEVIATIONS 76
21.0 DATA HANDLING AND RECORD KEEPING 77
21.1. SOURCE DATA AND CASE REPORT FORMS 77
21.2. DATA QUALITY ASSURANCE 77
21.3. RECORD RETENTION 77
22.0 PUBLICATION POLICY 77
23.0 REFERENCES 78

TABLES

[redacted]
Table 3. FLACC Scoring 48
Table 4. Table of Evaluations 56
Table 5. Table of Ear-related Adverse Event Severity 60
Table 6. Table of Other Events Adverse Event Severity 61
Table 7. Table of Adverse Event Causality 62
Table 8. Table of Hearing Threshold Change (Worsening) Classification 63

FIGURES

Figure 1. Iontophoresis Control Unit 22
[redacted]
Figure 3. Return Electrode Patch 23
Figure 4. Ear Plug Sizers 24
Figure 5. Current Ramp Profile 26
Figure 6. Schematic of Iontophoresis of the TM 26
Figure 7. Tusker Medical Tympanostomy Tube 27
Figure 8. Tube Delivery System 27
[redacted]
Figure 10. Faces Pain Scale-Revised 47
Figure 11. Schematic of Study Design Flow 55

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
FDA	Food and Drug Administration
FPS-R	Faces Pain Scale- Revised
FLACC	Faces, Legs, Arms, Cry, Consolability Scale
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
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

5.0 PROTOCOL SUMMARY

Brief Title:	OTTER; in-Office Tympanostomy Tube placemEnt in childRen
Working Title:	A prospective, single-arm, multicenter study to evaluate effectiveness and safety of tympanostomy tube placement using the TULA Iontophoresis and Tube Delivery Systems for children in an office setting
IDE Protocol	IDE G170193
Brief Summary:	The objective of this study is to evaluate effectiveness and safety of tympanostomy tube (TT) placement in children following local anesthesia in a physician's clinic setting (henceforth referred to as 'in-office'). Local anesthesia using a lidocaine-based anesthetic is delivered by the TULA Iontophoresis System (IPS) and TT placement is implemented by the TULA Tube Delivery System (TDS). 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 IPS is intended to anesthetize the tympanic membrane utilizing the 2% lidocaine HCl, 1:100,000 epinephrine solution. 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 (ie, not indicated for topical administration to the TM, nor for iontophoretic administration). [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 pivotal study will include up to 422 children ages 6 months through 12 years indicated for tympanostomy tube placement enrolled at approximately 15 to 25 investigational centers in the US and Canada.[i]

[redacted] Study enrollment and procedures will occur in two stages:

Stage 1: Stage 1 consists of tube placement procedures in the OR under general anesthesia. [redacted] each investigator will enroll 2 lead-in subjects in the operating room (OR) undergoing tube placement using the TDS (up to 100 subjects).

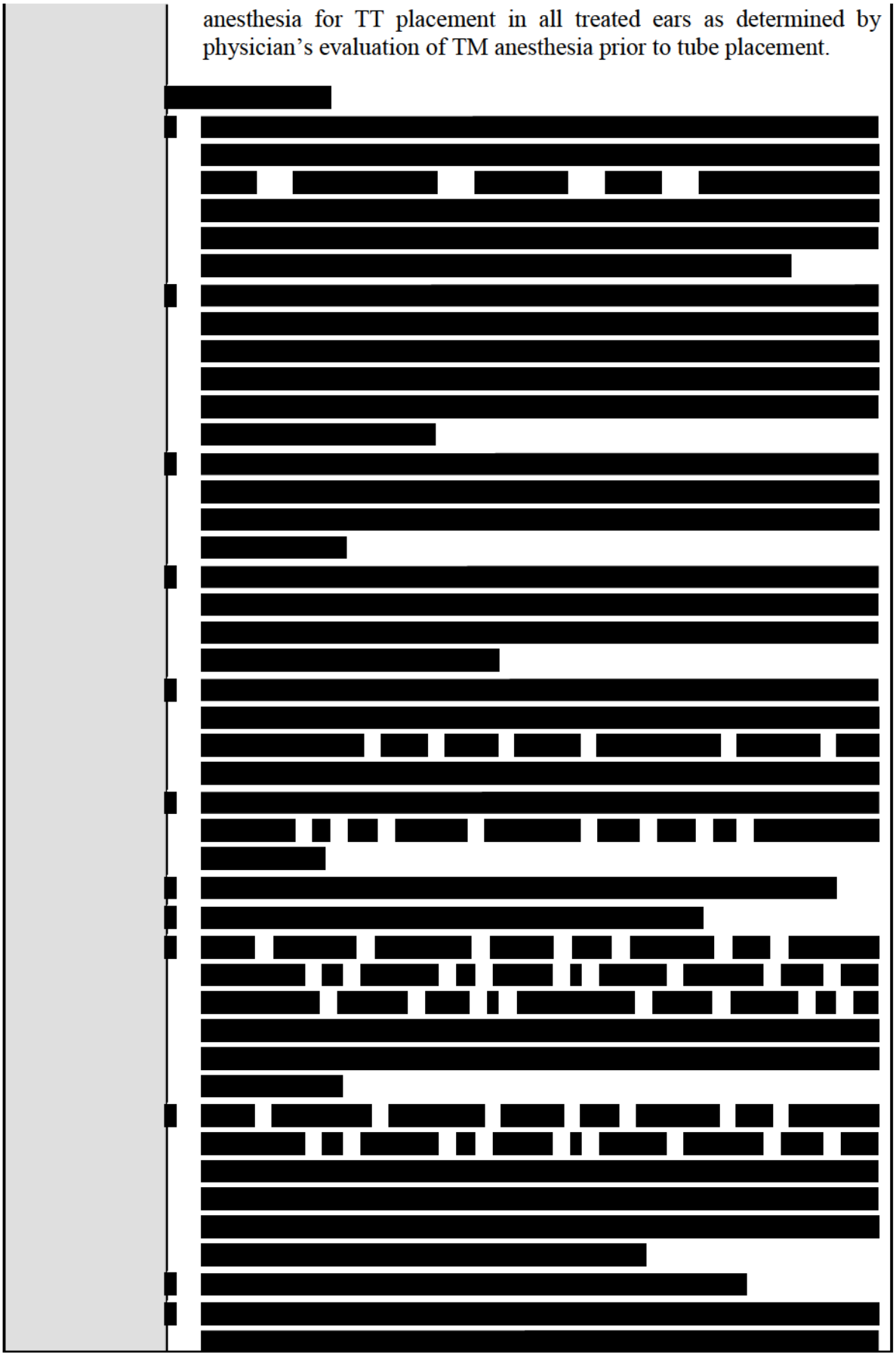
Stage 2: Stage 2 consists of in-office tube placement procedures using local anesthesia. [redacted] each investigator will enroll 2 lead-in subjects in-office undergoing tube placement using the TDS with local anesthesia facilitated by the Iontophoresis System (up to 100 subjects). Investigators may enroll into the pivotal cohort following completion of their lead-in procedures. The pivotal cohort will include 102 children ages 5 years and greater plus 120 children less than 5 years of age.

All pivotal and lead-in subjects will follow the same study protocol assessments and visit schedule consisting of a screening visit, procedure visit and a 3-week post-procedure follow-up visit. [redacted] In addition, subjects will return for follow-up examinations every 6 months following the procedure until the tube implants have extruded, up to 24 months post-procedure. Otologic examination, tympanometry and audiometry will be conducted at the screening visit for all subjects (OR and in-office). Additionally, subjects treated in-office with local anesthesia (lidocaine iontophoresis) will undergo a cranial nerve physician exam at screening. The in-office lead-ins and pivotal cohort procedure will consist of local anesthesia of the tympanic membrane using the TULA Iontophoresis System with the lidocaine solution. Following iontophoresis, anesthesia of the TM will be assessed and tympanostomy tube placement will be conducted in anesthetized ears using the TULA Tube Delivery System. Subjects will return for a follow-up visit 3-weeks

[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), and enrolled subjects who withdraw prior to the study procedure are not included in the enrollment subject counts presented herein. Further definition of subjects included in the analysis sets is provided in Section 13- Statistical Methods

	post-procedure for otoscopic examination, tympanometry and audiometric assessment for all subjects with the addition of the cranial nerve exam for in-office subjects only. Follow-up assessments for tube duration at 6, 12, 18 and 24 months will consist of otoscopic examination and tympanometry. Lead-in procedures will be analyzed separately from the pivotal pediatric cohort.
Study Design:	Study Phase: Pivotal No. of Centers: Minimum of 15, maximum of 25 investigational centers Number of Arms: Single Enrollment: Up to 422, including 222 pediatric subjects in the pivotal cohort, and up to 100 lead-in OR and up to 100 lead-in in-office subjects.
Safety Measures	Safety Evaluation will include the following assessments: • Otoscopic examination for visual inspection of external ear canal, TM condition at all visits (baseline, post-procedure and follow-up visits), with additional assessment of the myringotomy wound and tube at all protocol-specified follow-up visits. • Audiometry to assess hearing at baseline and at the 3-week post-procedure follow-up visit. • Tympanometry to assess tympanic membrane and middle ear conditions at baseline and at all protocol-specified follow-up visits. • Cranial nerve physical exam to assess cranial nerves CN VII (facial) and CN VIII (vestibulocochlear) at baseline, post-procedure and the 3-week post-procedure follow-up visit (in-office lead-in and pivotal subjects only). • Adverse events
Endpoints:	Primary Endpoints: • **Procedural Success:** Proportion of subjects in the pivotal cohort with successful placement of Tusker Medical tympanostomy tubes in all indicated ears in an office procedure • **Tube Placement Tolerability:** Mean subject-reported pain score following TDS tube placement using the Faces Pain Scale-Revised (FPS-R) (pivotal cohort children ages 5 and older only) Safety Endpoint: • **Safety:** Occurrence of adverse events, by subject Secondary Efficacy Endpoints: • **Tube Patency:** Tube Patency is the proportion of subjects in the pivotal cohort, in which a Tusker Medical tube was successfully placed, with functionally patent tube(s) in all successfully treated ears at the 3-week post-procedure follow-up visit. • **Tube Retention:** Tube Retention is the proportion of subjects in the pivotal cohort, in which a Tusker Medical tube(s) was successfully placed, with presence of a Tusker Medical tube across the TM in all successfully treated ears at the 3-week post-procedure follow-up visit. • **Anesthesia Effectiveness:** Proportion of subjects in the pivotal cohort, who completed iontophoresis for all indicated ears, with adequate

anesthesia for TT placement in all treated ears as determined by physician's evaluation of TM anesthesia prior to tube placement.



	[redacted]
Eligibility Criteria:	**Inclusion Criteria:** 1. Males or females at least 6 months old through 12 years old at time of consent 2. Indication for tympanostomy tube insertion per Clinical Practice Guideline[1] 3. Behavioral capacity and cooperative temperament to undergo an awake procedure, based on physician judgment *(not applicable to OR Lead-In subjects)* 4. Subject's parent/guardian and subject are able and willing to comply with the protocol and attend all study visits 5. Subject's parent/guardian and subject are able and willing to provide informed consent or assent as age appropriate
	Exclusion Criteria: 1. Significantly atrophic, retracted, bimeric, monomeric or atelectatic tympanic membrane 2. Perforated tympanic membrane 3. Otitis externa 4. Active or recent conditions of the tympanic membrane (eg, prior myringotomy with incomplete wound healing or re-epithelization) 5. Hemotympanum 6. Damaged/denuded skin in the auditory canal 7. 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 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 10. 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 *(not applicable to OR Lead-In subjects)* 11. Familial history of insensitivity to lidocaine or other local anesthetics (eg, history of inadequate anesthesia with dental numbing agents) *(not applicable to OR Lead-In subjects)* 12. Electrically sensitive medical support systems (eg, pacemakers, defibrillators, cochlear implants) *(not applicable to OR Lead-In subjects)* 13. Other conditions that would preclude performing the study procedure including iontophoresis system ear plug incompatibility. 14. 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.

	15. Subject is 4 years or older and not able to complete all baseline assessments. Subject is younger than 4 years and not able to complete all baseline assessments, not including audiometry.
Statistical Analysis	**Procedural Success:** The statistical test for the procedural success primary endpoint is a hypothesis test for the proportion of pivotal cohort subjects who achieve procedural success against a procedural success performance goal. The hypotheses $H_o : p \leq 68\%$ Vs. $H_a : p > 68\%$ will be tested using a Bayesian hierarchical model that estimates two different success probabilities, one for subjects 5 through 12 years old, the other for subjects between 6 months and 5 years of age. A gatekeeping strategy will be used. The first test will include all pivotal cohort subjects 5 through 12 years old. This will include 102 subjects ages 5 through 12 with evaluable data. [redacted] Once 120 subjects in the younger group (6 months to <5 years of age) have enrolled and have evaluable procedure data, and if the posterior probability that H_a is correct for the 102 older subjects exceeds 0.975 (similar to achieving a 1-sided p-value $\leq$ 0.025), then the younger group may be tested against the Procedural Success performance goal. [redacted] **Tube Placement Tolerability:** The statistical test for the tube placement tolerability primary endpoint is a hypothesis test using a standard classical t-test at the 0.025 significance level. The test against the performance goal is conducted on only the older children in the pivotal cohort, once the study has accrued evaluable data for 102 children ages 5 through 12 years old. The primary hypothesis is: $H_o: p_{5+} \geq 4.2$ vs. $H_a: p_{5+} < 4.2$ Where p_{5+} is the mean Tube Placement FPS-R score for subjects 5 through 12 years old.

6.0 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

6.1. 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.[2]

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.[3] 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. 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.[4] 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.[4] Over 95% of tympanostomy tube insertion procedures in children are performed in the operating room (OR) under general anesthesia.[4]

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.[ii]
- Premedication with oral midazolam may be provided to calm the child prior to parental separation.[5]
- After general anesthesia is attained, prophylactic analgesia to address post-operative pain such as rectal acetaminophen or intranasal fentanyl is typically provided.[6]
- 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.[7,8]
- 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.

[ii] 2017 ASA pre-operative fasting guidelines range restrict clear liquids for 2 hours, breast milk for 4 hours, cow's milk, formula and light meals for 6 hours and heavy or fatty meals for 8 hours.

- Minor adjustments are then often performed using standard otologic microinstruments, such as a Rosen pick or alligator forceps, to achieve optimal tube position.[9]
- Multiple attempts to place the tube may be required in a considerable number of cases.[7]

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.[10] Other anesthetics, such as EMLA cream (Eutectic Mixture of Local Anesthetics, lidocaine 2.5% and prilocaine 2.5%), lidocaine HCl injections, Bonain's Solution (cocaine hydrochloride, menthol, phenol) and tetracaine injections are used less frequently.[11,12,13] 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.[14,15] 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.[16] 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.[17] A recent publication demonstrated a significant loss in brain white matter for children undergoing brief anesthetic exposures (30% of the study sample was tympanostomy procedures) as compared to non-exposed controls.[18] Another recent study shows that a single exposure to general anesthetic from common and minor surgical procedures is associated with small but statistically-significant increased risks of mental disorder diagnosis, developmental delay, and attention deficit hyperactivity disorder.[19] FDA recently issued a Drug Safety Communication warning that repeated use of general anesthetic and sedation drugs, or use for greater than three hours, in young children may affect the development of children's brains.[20] While anesthetic exposure during tympanostomy tube procedures is usually brief, approximately 30% of children receiving tubes reported to require a second procedure.[21,22] While studies suggest a link between general anesthesia exposure and neurodevelopment, the long-term effects resulting from brief exposures to general anesthetics are unknown.

In addition, both pre-operative anxiety and post-operative stress behaviors are common in children. A reported 50-75% of children who undergo anesthesia develop significant behavioral stress before surgery.[23] 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% 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.[24]

The list below reviews reported distress, pain and medical therapies reported for pediatric tympanostomy procedures under general anesthesia.

Pre-Operative:

- Pre-operative anxiety is common and not insignificant, likely exacerbated by the requirements for fasting. For children aged 2 to 10 years old undergoing common elective outpatient procedures, Kain measured pre-operative anxiety at 37 (on a 100-point Visual Analogue Scale (VAS)), which rose to 57 upon parental separation as the child was taken to the OR.[19] To address pre-operative anxiety before tympanostomy procedures, many institutions regularly administer midazolam to the child.[5] Other techniques have been employed in the operating room to reduce pre-operative anxiety such as music, videos, and presence of a favorite toy.

Induction:

- Children often express distress behaviors during induction of anesthesia for outpatient elective surgery. Even with a parent present for anesthesia induction, Chorney demonstrated that greater than 40% of children aged 2-10 years old display clear distress behaviors during induction, with 17% displaying significant distress and more than 30% of children resisting anesthesiologists during induction.[25] On a visual analogue scale, parents of children (5.8 year-old mean) undergoing outpatient surgery rated the child's induction anxiety as a mean score of 40.0 (out of 100).[26] Sadeghi et al has shown some success in reducing pre-operative pediatric anxiety by having the parent present during induction.[27]

Intra-Operative:

- Despite the brevity of the procedure, intra-operative complications occur from the administration of the general anesthetic for pediatric tympanostomy procedures. Notably, laryngospasm (0.8%), desaturation (0.3%), dysrhythmia (0.2%-1.8%), severe airway obstruction (1.4%), intra-operative vomiting (0.4%) and mild airway obstruction (12%) have been reported in pediatric tympanostomy tube procedures performed under general anesthesia.[14,15]
- In addition to the general anesthetic, it is common practice at many institutions to administer additional systemic agents before pediatric tympanostomy procedures to control nausea and post-operative pain. For example, standard practice at Children's Hospital of Philadelphia (CHOP) is to administer systemic ketorolac, fentanyl, or both.[28]

Post-Operative Recovery In Hospital/ASC:

- 91% of children (2-11 years old) demonstrate distress behavior in recovery after elective outpatient surgery.[29]
- Despite receiving rectal acetaminophen and intra-nasal dexmedetomidine or fentanyl and half the subjects receiving oral midazolam, FLACC scores after outpatient tympanostomy surgery for children aged 1 to 8 years old ranged from 2.8-4.8 (out of a total possible score of 10) fifteen minutes after arrival to the recovery ward.[6]
- Emergence agitation, defined as *at least three minutes of thrashing behavior requiring restraint*, is seen in 27-57% of children (mean age 2.6-3.5 years old) after tympanostomy tube procedures.[30]
- After bilateral tympanostomy tube placement, 13-27% of children aged 9 months to 6 years old vomit during recovery.[31]
- Administration of opioids occurs in some facilities to address post-operative distress/pain. For example, a recent large study from Children's Hospital of Philadelphia shows oxycodone administration in 18% of children (6 months to 7 years old) in the recovery room after tube placement.[23] In British Columbia's Children's Hospital, 10% of children (aged 1.4 to 6 years old) received codeine in the recovery room, despite high-dose (40 mg/kg) oral acetaminophen received by all patients pre-operatively.[32]

Post-Operative Recovery at Home:

- After elective outpatient surgery, Kain demonstrated that 67% of children aged 1-7 years old exhibit new negative behaviors 1 day after surgery, with 45% continuing to demonstrate negative behavior changes 2 days after surgery.[33] In 23% of children, these behaviors persisted 2 weeks after surgery. The behaviors included waking up crying, temper tantrums and an increased fear of doctors and hospitals. Similarly, Kotiniemi demonstrated behavioral problems after routine ENT surgery in 61% of children aged 2-10 years old, with 32% persisting to 1 month after surgery.[34]
- After outpatient bilateral tympanostomy procedures at the Children's Hospital of Philadelphia, 29-52% of children (9 months to 6 years old) experienced vomiting within the first 24 hours.[26]

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. 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 data from this study will help inform whether the TULA procedure is successful in enabling a low-distress procedure with a favorable safety profile.

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 lidocaine and epinephrine into the tissue.

7.0 STUDY DEVICES

Tusker Medical, Inc. has an Iontophoresis System that drives ions of lidocaine and epinephrine into the tympanic membrane to provide local anesthesia to facilitate tympanostomy tube insertion. 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]

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 pediatric 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

The handheld Iontophoresis Control Unit (*Control Unit*) is a single-use microprocessor-controlled direct current generator, as shown in **Figure 1**. 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.

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. The IPS 2.0 includes a '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 nominal charge/dose is delivered.

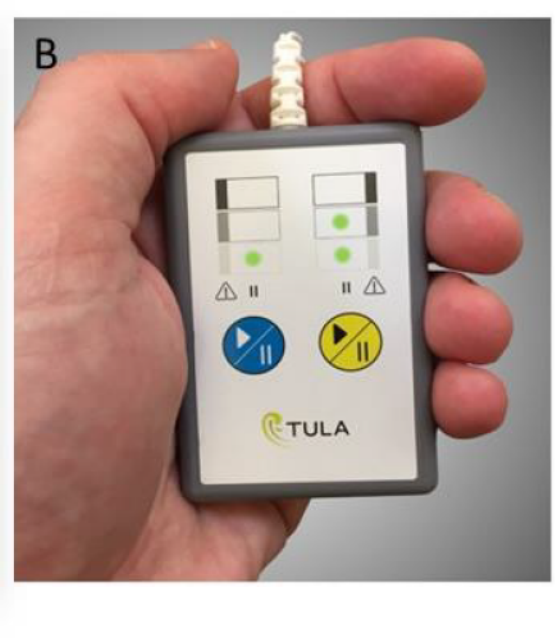


Figure 1. Iontophoresis Control Unit

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*. [redacted] 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]

[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.

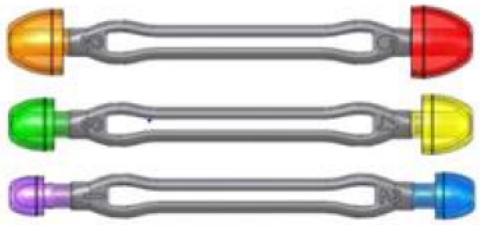


Figure 4. Ear Plug Sizers

Iontophoresis System Safety Features

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

- [redacted]

- [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]

- [redacted]

- [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 yellow or blue 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. The IPS 2.0 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, the device tracks overall charge and accordingly adjusts delivery time, ensuring the total charge/dose delivered is the same as when the Reduce feature is not used. 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.

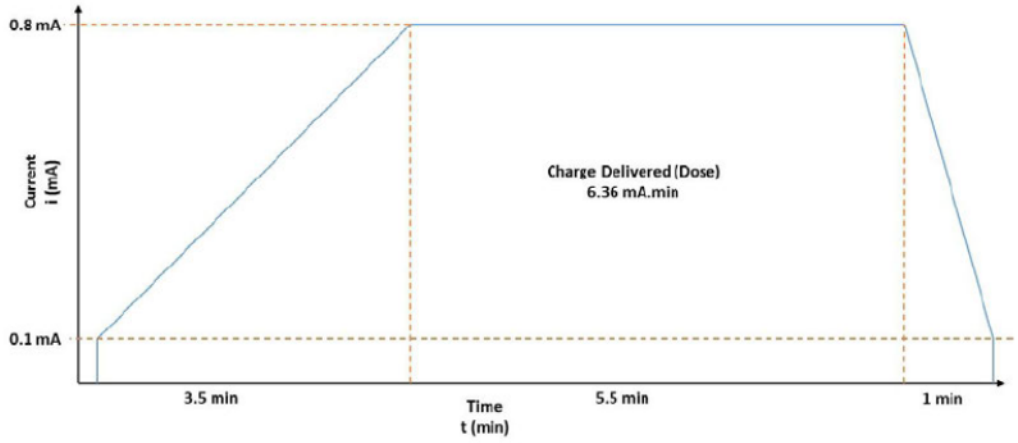


Figure 5. Current Ramp Profile

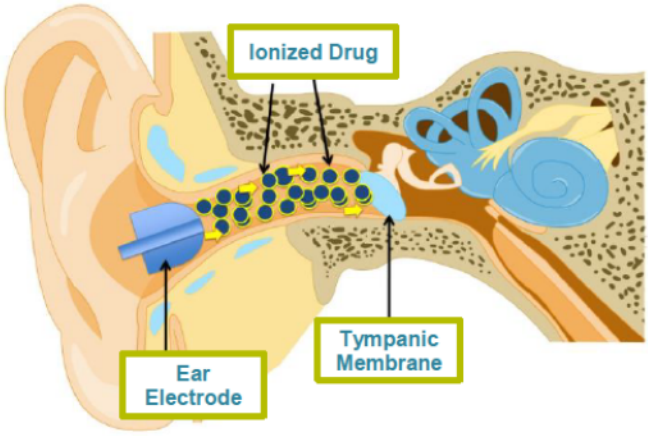


Figure 6. Schematic of Iontophoresis of the TM

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 or tilting. The surgeon confirms drug removal from the ear canal by direct visualization using an operating microscope.

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.

[redacted]

[redacted]

8.0 STUDY DRUG

The iontophoresis will be performed using 2% lidocaine HCl/1:100,000 epinephrine [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 CIB007001.

[redacted]

[redacted]

[redacted]

[redacted]

9.0 TUSKER MEDICAL CLINICAL EXPERIENCE

[redacted]

[redacted] The Investigator's Brochure (CIB007001) provides a complete summary of the prior clinical data.

10.0 STUDY DESIGN

10.1. 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 objective of this study is to evaluate effectiveness and safety of tympanostomy tube placement using the TULA Tube Delivery System following local anesthesia of the tympanic membrane using a lidocaine-based anesthetic solution and the TULA Iontophoresis System in awake, unsedated, unrestrained children in a physician's office setting to support a marketing application.

10.2. Overall Study Design – Phases and Enrollment

This study is a prospective, single-arm, multicenter evaluation of safety and effectiveness of iontophoresis using the IPS and TDS for TT placement in-office for children indicated for tympanostomy tube placement.

[redacted] Study enrollment and procedures will occur in two stages.

Stage 1 (OR Lead-In Cohort): Stage 1 consists of tube placement procedures in the OR under general anesthesia. [redacted] each investigator will enroll 2 lead-in subjects in the operating room (OR) undergoing tube placement using the Tube Delivery System to place the tympanostomy tube(s) under general anesthesia (ie, no lidocaine iontophoresis). Stage 1 is comprised of the OR Lead-In Cohort (up to 100 subjects; further described in **Section 11.2**).

Stage 2 (In-Office Lead-In Cohort and Pivotal Cohort): Stage 2 consists of in-office procedures using both the lidocaine Iontophoresis System and the Tube Delivery System for the in-office tube placement procedure, including both the Office Lead-In Cohort and the Pivotal Cohort. [redacted] each investigator will enroll 2 lead-in subjects in-office undergoing tube placement using the TDS with local anesthesia facilitated by the Iontophoresis System (up to 100 subjects in the Lead-In Office Cohort). Investigators may enroll into the Pivotal Cohort following completion of their lead-in procedures. The pivotal cohort will include 222 children (ages 6 months through 12 years, inclusive) with evaluable data indicated for tympanostomy tube placement enrolled

at up to 25 investigational centers (minimum of 15 centers).[iii] The pivotal phase will include 102 children ages 5 years and older, and 120 children less than 5 years of age with evaluable data.

All pediatric study subjects will follow the same study protocol assessments, plus cranial nerve exam for in-office subjects only, and visit schedule consisting of screening, procedure and a 3-week post-procedure follow-up visit. In addition, subjects will return for follow-up examination every 6 months following the procedure until the tube implants have extruded, up to 24 months post-procedure. The in-office procedure will consist of local anesthesia of the tympanic membrane using the TULA Iontophoresis System with lidocaine and epinephrine anesthetic solution. Following iontophoresis, anesthesia of the TM will be assessed and tympanostomy tube placement will be conducted in anesthetized ears using the TULA Tube Delivery System. OR lead-in procedures conducted with general anesthesia will consist of tympanostomy tube placement using the Tube Delivery System.

Safety will be assessed through reporting of adverse events, otoscopic examination, cranial nerve physical exam, tympanometry and audiometry.

10.3. Design of the Pivotal Study Phase

The pivotal phase of the study aims to confirm safety, and determine whether the in-office tube placement procedure achieves an acceptable procedural success rate and acceptable tube placement tolerability. The pivotal cohort will consist of a sample of 222 children including 102 children age 5 through 12 years old, and 120 children less than 5 years of age.[iv]

The study includes two primary endpoints each of which must be successful for the trial to be considered successful. The first primary endpoint, Procedural Success, is the proportion of pivotal cohort subjects with Tusker Medical tympanostomy tubes placed in all indicated ears in an office procedure. The statistical test for the Procedural Success primary endpoint is a hypothesis test against a procedural success performance goal. The performance goal for Procedural Success is further described in **Section 10.3.1**. The second primary endpoint, Tube Placement Tolerability, is the mean subject-reported pain score following TDS tube placement using the Faces Pain Scale-Revised (FPS-R) (pivotal cohort subjects ages 5 and older only). The statistical test for the Tube Placement Tolerability primary endpoint is a hypothesis test against a tube placement tolerability performance goal. The performance goal for Tube Placement Tolerability is further described in see **Section 10.3.1**.

[redacted] The test against the Procedural Success performance goal occurs in two steps:

[iii] 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), and enrolled subjects who withdraw prior to the study procedure are not included in the enrollment subject counts presented herein. Further definition of subjects included in the analysis sets is provided in Section 13-Statistical Methods.

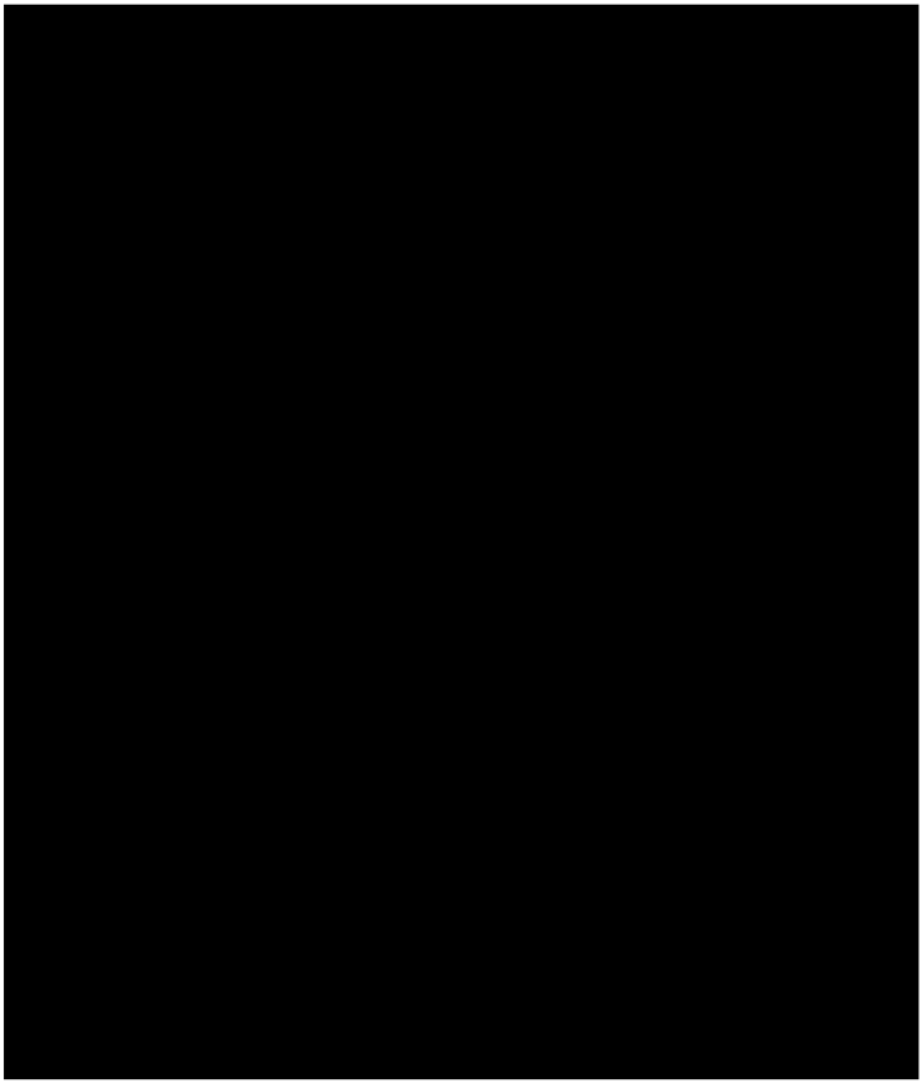
[iv] Ages 5 through 12 years is inclusive of children reaching their 5th birthday, but not yet reaching their 13th birthday. Ages 6 months through < 5 years is inclusive of children reaching their 6 month birthday, but not yet reaching their 5th birthday.

1) The initial test against the performance goal is conducted on the older children in the pivotal cohort, once the study has accrued evaluable data for 102 children ages 5 through 12 years of age. [redacted] The older child group will be tested against the Procedural Success performance goal using a Bayesian hierarchical algorithm designed to borrow information from the enrolled younger children as appropriate given the performance results at the time of the first test. [redacted] If the older child group achieves the performance goal, the second test is applied as in step 2.

2) Once the younger group achieves 120 evaluable subjects, they will be tested against the Procedural Success performance goal. The 102 older (5-12 years old) children are included in the Bayesian hierarchical model used to evaluate the younger subjects against the performance goal.

The second primary endpoint, Tube Placement Tolerability, will be tested for the older group only at step 1, above, at time of the initial test for Procedural Success for the 102 older children.

[redacted]



[redacted]

[redacted]

[redacted]

10.4. Study Population

Stage 1 of the study consists of tube placement procedures in the OR under general anesthesia. [redacted] each investigator will enroll 2 lead-in subjects in the operating room (OR) undergoing tube placement using the TDS (up to 100 subjects).

Stage 2 consists of in-office tube placement procedures using local anesthesia. [redacted] each investigator will enroll 2 lead-in subjects in-office undergoing tube placement using the TDS with local anesthesia facilitated by the Iontophoresis System (up to 100 subjects). Investigators may enroll into the pivotal cohort following completion of their lead-in procedures. The pivotal cohort will include 102 children ages 5 years and greater plus 120 children less than 5 years of age (222 children with evaluable data total).

10.4.1. 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 13.0** Statistical Methods provides further definition of subjects included in the analysis sets.

10.4.2. Study Cohort Definitions

10.4.2.1. Lead-In OR Cohort

The Lead-In OR Cohort will consist of all children who underwent a lead-in procedure in the OR. The Lead-In OR Cohort safety and effectiveness data will be analyzed and presented separately.

10.4.2.2. Lead-In Office Cohort

The Lead-In Office Cohort will consist of all children who underwent a lead-in procedure in-office. The Lead-In Office Cohort safety and effectiveness data will be analyzed and presented separately.

10.4.2.3. Pivotal Cohort

The Pivotal Cohort will consist of children who underwent an in-office procedure using the TULA System (not including Lead-In subjects). The Pivotal Cohort safety and effectiveness data will be analyzed and presented separately.

10.5. Primary Endpoints

There are two primary endpoints for the study. The first primary efficacy endpoint is Procedural Success, defined as:

Procedural Success: Proportion of subjects in the pivotal cohort with successful placement of Tusker Medical tympanostomy tubes in all indicated ears in an office procedure.

[redacted]

If both ears of a subject are indicated for TT placement, the procedure must be successful in both ears for the procedure to be counted as a success on a subject-level for the Procedural Success primary efficacy endpoint. If either ear does not receive a tube, the procedure is not considered a success. If a subject requires only a unilateral tube, the procedure is considered a success when the indicated ear has received the tube. The procedural success definition is aligned with the desired clinical outcome; the child has Tusker tubes placed in all indicated ears while avoiding general anesthesia and an OR visit. The statistical test for the pivotal cohort primary endpoint is a Bayesian hypothesis test against a procedural success performance goal.

The second primary efficacy endpoint is Tube Placement Tolerability, defined as:

Tube Placement Tolerability: Mean subject-reported pain score following TDS tube placement using the Faces Pain Scale-Revised (FPS-R) (pivotal cohort children ages 5 and older only).

[redacted]

If both ears of a subject are indicated for tympanostomy tube placement, the tube placement pain score is collected after the second ear tube placement is completed (one tube placement pain score per subject). The FPS-R 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.

[redacted]

[redacted]

[redacted] Only completers, ie, subjects with FPS-R scores after successful tube insertion in all indicated ears, will be included in the primary analysis.

10.6. 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 in-office subjects in which the lidocaine solution was introduced into the ear, or introduction of TDS in ear for OR lead-in subjects) (see **Section 13.2.3**), [redacted]

Safety data will be presented separately as follows:

- Lead-In OR Cohort
- Lead-In Office Cohort*
- Pivotal Cohort*

[redacted]

10.7. Secondary Effectiveness Endpoints

10.7.1. Tube Patency

Tube Patency: Tube Patency is the proportion of subjects in the pivotal cohort, in which a Tusker Medical tube was successfully placed, with functionally patent tubes in all successfully treated ears at the 3-week post-procedure follow-up visit.

The statistical test for the pivotal cohort Tube Patency endpoint is a hypothesis test against a Tube Patency performance goal.

10.7.2. Tube Retention

Tube Retention: Tube Retention is the proportion of subjects in the pivotal cohort, in which a Tusker Medical tube was successfully placed, with presence of a Tusker Medical tube across the tympanic membrane in all successfully treated ears at the 3-week post-procedure follow-up visit.

The statistical test for the pivotal cohort Tube Retention endpoint is a hypothesis test against a Tube Retention performance goal.

10.7.3. Anesthesia Effectiveness

Anesthesia Effectiveness: Proportion of subjects in the pivotal cohort, who completed iontophoresis for all indicated ears, with adequate anesthesia for TT placement in all treated ears as determined by physician's evaluation of TM anesthesia prior to TT placement.

The statistical test for the pivotal cohort Anesthesia Effectiveness endpoint is a hypothesis test against an Anesthesia Effectiveness performance goal.

[redacted]

[redacted]

[redacted]

10.9. Inclusion Criteria

1. Males or females at least 6 months old through 12 years of age at time of consent.[viii]
2. Indication for tympanostomy tube insertion per Clinical Practice Guideline (see **Section 11.4.1 Diagnosis)** [1]

[viii] Age 12 includes children who have not yet had their 13th birthday.

3. Behavioral capacity and cooperative temperament to undergo an awake procedure, based on physician judgment (*not applicable to OR Lead-In subjects*)

4. Subject's parent/guardian and subject are willing and able to comply with the protocol and attend all study visits.

5. Subject's parent/guardian and subject are willing and able to provide informed consent or assent as age appropriate.

10.10. Exclusion Criteria

1. Significantly atrophic, retracted, bimeric, monomeric or atelectatic tympanic membrane

2. Perforated tympanic membrane

3. Otitis externa

4. Active or recent conditions of the tympanic membrane (eg, prior myringotomy with incomplete wound healing or re-epithelization)

5. Hemotympanum

6. Damaged/denuded skin in the auditory canal

7. 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

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

10. 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 (*not applicable to OR Lead-In subjects*)

    *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.

11. Familial history of insensitivity to lidocaine or other local anesthetics (eg, history of inadequate anesthesia with dental numbing agents). (*not applicable to OR Lead-In subjects*)

12. Electrically sensitive medical support systems (eg, pacemakers, defibrillators, cochlear implants) (*not applicable to OR Lead-In subjects*)

13. Other conditions that would preclude performing the study procedure including ear plug incompatibility

14. 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

15. Subject is 4 years or older and not able to complete all baseline assessments. Subject is younger than 4 years and not able to complete all baseline assessments, not including audiometry.

Ear-specific exclusions (# 1-9, 13) apply to all indicated ears. Subjects may be indicated for unilateral or bilateral tube placement as described in **Section 11.4.1**. If a potential subject has both ears indicated for TT placement, but one ear does not meet the eligibility criteria, the subject is not eligible for the study because they would require an alternate treatment for the ineligible ear.

Investigators will document additional information to provide the rationale for exclusion for subjects not meeting inclusion criterion 3 (Behavioral capacity and cooperative temperament to undergo an awake procedure, based on physician judgment).
If a previously-determined eligible subject presents on the procedure day with a change in condition, such as an acutely infected ear or behavior non-compliance, the investigator may use clinical judgment to determine whether the condition as presented precludes performing the study procedure (Exclusion 13). The physician also has the option to re-schedule the procedure if the condition is transient.

11.0 STUDY PROCEDURES

11.1. Investigator Training

Investigators will be asked to refer to the drug package insert, device Instructions For Use (IFU) and the Investigator's Brochure 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.

11.2. Lead-In Procedures

Each investigator will be required to enroll and conduct lead-in procedures prior to enrolling subjects to the pivotal cohort. Subjects enrolled to the lead-in cohorts must meet the same eligibility criteria and must complete the same protocol-required procedures and assessments as the pivotal cohort; however, their data will be separately analyzed and reported. Subjects undergoing OR procedures using general anesthesia must be suitable candidates for a surgical procedure under general anesthesia per Investigator's standard practice.

The lead-in procedure criteria are summarized below:
- 2 subjects ages 6 months through 12 years in the OR under general anesthesia using the TULA TDS (Stage 1), and

- 2 subjects ages 6 months through 12 years in-office using the TULA Iontophoresis and Tube Delivery Systems (conducted after Stage 2 approval).

Any investigator enrolling pediatric pivotal cohort in-office procedures must first complete OR lead-in procedures followed by lead-in in-office procedures for children. [redacted] Additional optional lead-in subjects may be enrolled at Investigator or Sponsor discretion in any of the categories listed above. Such selection must occur prior to enrollment of the subject into the study.

[redacted]

11.4. Evaluation Methods

11.4.1. Diagnosis

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.

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 caregiver 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 parent/guardian. 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.
- *Unilateral or bilateral* TT insertion in at-risk children with unilateral or bilateral OME, *respectively,* that is unlikely to resolve quickly as reflected by a type B (flat) tympanogram or persistence of effusion for 3 months or longer (chronic OME). At risk children have increased risk for speech, language or learning problems from otitis media because of baseline sensory physical, cognitive or behavioral factors.

In this study, the caregiver 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.

11.4.2. 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. Medications administered or prescribed prior to, during or post-operatively (including OR procedures) will be documented through study exit.

11.4.3. Cranial Nerve Physical Exam

A standard cranial nerve physical exam will be employed for all subjects enrolled for in-office procedure at screening, after the procedure and at the 3-week post-procedure follow-up visit to identify any potential adverse effects related to the lidocaine iontophoresis anesthesia component of the procedure. [redacted] Any abnormalities will be recorded at screening, procedure and at the follow-up visit and the subject will be assessed for any adverse events. [redacted]

11.4.4. Otoscopy

An otoscopic exam will be conducted for both ears in all subjects at screening, for all ears intended for treatment at procedure and for all treated at the follow-up 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. Ear cleaning at the screening visit is required. Patients who are uncooperative during ear exam and ear cleaning at screening are not eligible study candidates.

The exam will be used to confirm eligibility, to assess the ear canal and TM for changes or adverse effects, and to inspect for residual drug prior to tube placement. In addition, appearance and patency of the tympanostomy tube and appearance of the myringotomy wound will be evaluated post-procedure and at the post-procedure follow-up visits. Presence or absence of middle ear effusion will be assessed.

The screening otoscopic exam may be conducted up to 28 days prior to procedure. Otoscopic examination is considered standard of care for this patient population and may be obtained prior to study informed consent as a screening assessment within 28 days prior to procedure.

11.4.5. Tympanometry

Standard tympanometry of both ears will be employed to assess TM function at screening (within 28 days prior to procedure) and at all follow-up visits for all treated ears. Tympanometry data recorded will include tympanogram type, ear canal volume, peak pressure, and static acoustic immittance 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, the subject will be considered a screening failure, and will not be eligible for the study. Tympanometry is considered standard of care for this patient population and may be obtained prior to study informed consent as a screening assessment within 28 days prior to procedure.

11.4.6. Audiometry

Audiometry will be employed to evaluate hearing status in each ear at screening (within 28 days prior to procedure) and at the 3-week post-procedure follow-up visit for all subjects age 4 years or older. Threshold testing will be conducted using air conduction and bone conduction at a minimum of 500, 1000, 2000 and 4000 Hz, and air conduction only at 8000Hz. Study sites will make efforts to measure hearing thresholds at all 5 frequencies. For younger subjects (less than 4 years of age), clinical study sites will attempt to collect audiometry at screening at a minimum of two frequencies for both air conduction (AC) and bone conduction (BC). The clinical study site audiologist will determine the most appropriate test method for each subject (visual reinforcement audiometry (VRA), conditioned play audiometry (CPA) or conventional audiometry). The method used at screening will be used for all follow-up assessments.

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

11.4.7. Anesthesia Effectiveness

Following iontophoresis, the Investigator will use physician judgment to assess whether the TM is adequately anesthetized for the tympanostomy tube placement procedure by evaluating subject response to a gentle tap of the TM with a dull otologic instrument,

[redacted]

[redacted] The tap will occur on the anterior half of the TM at the location where the tympanostomy tube will be placed. 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.

11.4.8. Tolerability (FPS-R)

The Faces Pain Scale-Revised (FPS-R) (**Figure 10**) is an instrument for assessing procedural pain validated for use in children 4 years of age and older. This study will employ the FPS-R for children in the older cohort only (age 5 years and greater). Subjects ages 5 years and older will rate their discomfort following TDS tube placement (after second ear, if bilateral treatment) using the FPS-R. If optional suction is performed, the subject will rate their discomfort following suction of both ears (if indicated bilaterally). In addition, an FPS-R score will be collected from the children approximately 5 minutes after completion of tube placement, or after completion of suction (whichever intervention is last). A baseline measure of ear discomfort will be assessed after ear cleaning (if required) and prior to Earset placement.

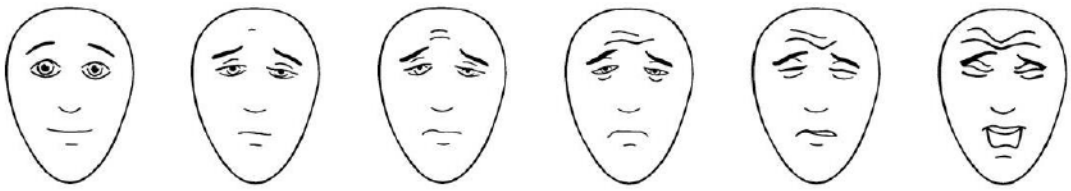


Figure 10. Faces Pain Scale-Revised

If a subject discontinues the procedure prior to completion of tube placement, an FPS-R score will be collected for the discontinued procedure.

11.4.9. Tolerability (FLACC)

The FLACC (Face, Legs, Activity, Cry, Consolability) scale is a method to evaluate behavioral distress for children as young as 2 months or individuals that are unable to communicate their pain.[61] The FLACC is a valid and reliable pediatric observational measure that ranges from low (0) to high (10) distress. The FLACC is recommended in the PedIMMPACT consensus statement and is a widely used observational measure of pediatric behavioral pain and distress.[62]

The scale has five categories which are each assigned a score of 0, 1 or 2 by an evaluator, as shown in **Table 3**.

Table 3. FLACC Scoring

Category	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, uninterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting, back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

FLACC scoring will be performed using the videos of the children's procedures, and will evaluate distress observed in the 6 procedural phases: pre-procedure otoscopy, iontophoresis earset installation/earset filling, iontophoresis, eardrum tap/tube placement, suction if suction is performed, post-procedure. A FLACC score will also be assigned to the overall procedure. Trained video evaluators (coders) at a centralized core lab (to ensure consistency in grading) will code a randomly selected sample of the study videos to assess interrater reliability to assess agreement across all 5 FLACC categories. [redacted]

[redacted]

11.5. Subject Recruitment and Informed Consent

Consecutive potentially-eligible patients presenting to the study site and for whom tympanostomy tube insertion is recommended will be offered the opportunity to participate in the study by the investigator. 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 and their caregivers 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 and/or subject's parent/guardian's satisfaction and will allow ample time for the subject and/or parent/guardian to read the informed consent form (and/or assent as applicable) 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 and/or their parent/guardian will be informed through both verbal and written information, and will sign an informed consent, or assent as applicable, according to local requirements, which states that any withdrawal from the study will neither prejudice nor in any way affect their future treatment. Subject (or legally authorized representative) consent and/or assent 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/assent form(s) will be given to the subject and/or their parent/guardian and the original(s) 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 and/or assent form(s) as appropriate.

All individuals that sign the informed consent, or assent as applicable, will be considered enrolled subjects.

[redacted]

11.6. 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 (in-office procedure subjects only)
3. Microscopic otoscopy with ear cleaning
4. Tympanometry and Audiometry (in either order)
5. Inclusion/Exclusion

11.7. Procedure

11.7.1. Otoscopic Examination and Ear Preparation

An otoscopic exam will be conducted using a microscope for both ears in all subjects 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.

11.7.2. 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.

11.7.3. Anesthetic Solution Preparation

The 2% lidocaine/1:100,000 epinephrine anesthetic solution will be warmed to body temperature prior to instillation of approximately 1-2mL into each ear canal to minimize the caloric effect.

11.7.4. 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.

The Electrode Cable is snapped to the Return Electrode Patch. The Electrode Cable connects the Earsets and the Control Unit. 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.[65] Category 4 also includes visible blister or burn. The location will be assessed again following iontophoresis.

In the event that drug has been introduced into the ear and iontophoresis was not initiated, the subject will return for a follow-up visit 2 to 5 days post procedure to complete all assessments required at the 3-week visit since drug will have been introduced into the ear. This subject is included in the Safety Analysis Set, but is not considered a discontinued procedure since iontophoresis was not initiated and is therefore not included in the Full Analysis Set. The subject may then be exited from the study after the follow-up visit if no unresolved device, procedure or drug-related adverse events are present. If there are unresolved adverse events, the subject must also return for the scheduled 3-week follow-up visit. However, if the subject plans to undergo tube placement in the OR, the subject's subsequent procedure success will be documented as described in **Sections 10.8.5 and 11.7.10**. This subsequent procedure must take place within 2 months of the study procedure. No additional follow-up is required following this non-study tube placement procedure.

11.7.5. Start of Iontophoresis

To begin anesthesia, the Control Unit buttons 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 progress 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 signal when complete. The IPS 2.0 also includes a '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 nominal charge/dose is delivered.

11.7.6. 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 Investigator will inspect the ear canal and TM using an operating microscope to directly visualize the anatomy confirm removal of residual drug in the ear canal.

The return electrode location will be assessed for erythema 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.[67] Category 4 also includes visible blister or burn. Scores of 3 or greater will be considered adverse events.

11.7.7. Post-Iontophoresis Anesthesia Effectiveness

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 evaluate subject sensation and whether anesthesia is adequate for tympanostomy tube placement. Pain resulting from inadequate anesthesia after TM tap as judged by the surgeon will be recorded as an adverse event reflecting an unacceptable level of subject discomfort that prevents the surgeon from attempting to insert the tube. [redacted]

11.7.8. Tympanostomy Tube Placement

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. [redacted]

Following TDS tube placement, the subject will report their post-tube placement ear discomfort (on a by-subject basis) using the FPS-R.

The investigator may elect to use suction only after placement of TT in all indicated ears. A low level of suction may be used to gently remove fluid through the placed tube, taking care to not dislodge the tube. Use of suction will be recorded. Following suction, the subject will report their post-suction ear discomfort (on a by-subject basis) using the FPS-R.

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.

11.7.9. Post-Procedure Otoscopy and Cranial Nerve Exam

An otoscopic exam will be conducted post-procedure. The otoscopic examination will be used to visually examine the condition of the external ear canal, TM and tube. A cranial nerve physical exam will also be conducted pre- and post-procedure for all in-office subjects.

11.7.10. Unsuccessful Procedures

If the in-office procedure is not a success and the physician refers the subject for traditional OR TT placement, the Investigator will document the OR procedure TT placement success. Reasons for any OR procedural failures (of TT placement) will be documented. The OR procedure must take place within 2 months of the first in-office procedure. The subject must complete a post-procedure follow-up visit after the failed in-office procedure, at the protocol specified 3-week follow-up visit, or earlier if the OR procedure is planned prior to the 3-week visit. If no Tusker tube was placed, no additional follow-up visit is required following the subsequent procedure. If a Tusker tube was placed, the subject should follow the protocol-specified follow-up visit schedule to assess safety of the Tusker tube.

[redacted]

11.9. 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, tube retention and patency.

3. The subject will complete the audiometry and tympanometry, and cranial nerve physical exam (for in-office subjects only).

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

11.10. 6, 12, 18 and 24-month Post-Procedure Follow-Up Visits (+/- 28 days)

1. All subjects are required to return for additional follow-up visits through confirmation of tube extrusion (both ears if bilateral tube placement).

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

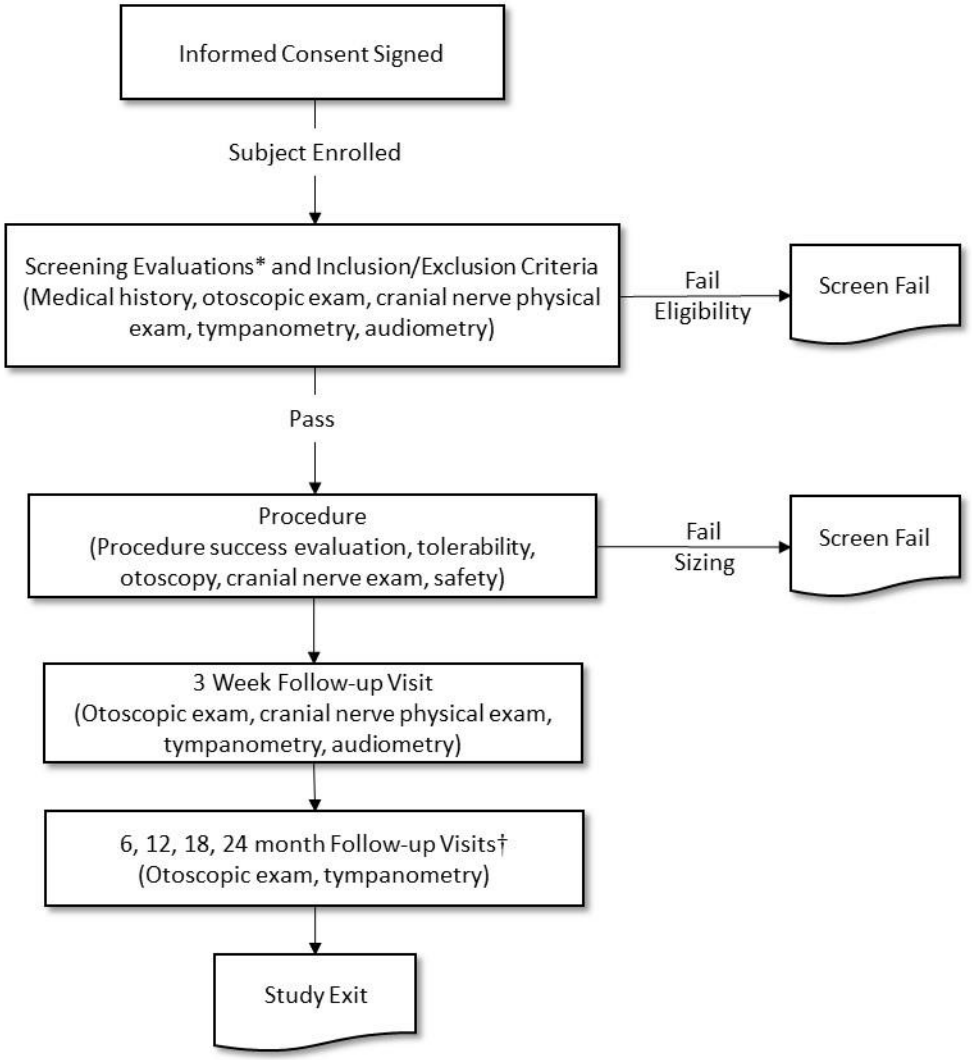
3. The subject will complete tympanometry. If audiometry is indicated, the study will collect audiometric data however there is no study requirement for audiometry or audiometry method for follow-up visits subsequent to the 3-week visit.

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

5. The subject will be exited from the study following confirmation of tube extrusion or completion of the 24 month visit if tube remains in place.

11.11. Summary – Study Flow and Study Evaluations

The flow of subject participation, visits and evaluations is depicted as a schematic in **Figure 11**.



*Otoscopic examination, tympanometry and audiometry are considered standard of care for this patient population. Data obtained from these assessments within 4 weeks prior to study informed consent may be included as screening assessments.

† If tube(s) have been confirmed to have extruded, no additional follow-up visits are required and the subject may exit prior to the 24 month visit.

Figure 11. Schematic of Study Design Flow

The schedule of evaluations for each study visit is presented in **Table 4**.

Table 4. Table of Evaluations

Evaluation	Screening	Procedure	3 Weeks (-/+ 7 days)	6, 12, 18, 24 months† (-/+ 28 days)
Informed Consent	✓			
Medical History	✓			
Cranial Nerve Physical Exam*	✓	✓	✓	
Concomitant Medications	✓	✓	✓	✓
Inclusion/ Exclusion Criteria	✓	✓		
Otoscopy	✓ (**within 28 days prior to Procedure)	✓	✓	✓
Tympanometry	✓ (**within 28 days prior to Procedure)		✓	✓
Audiometry	✓ (**within 28 days prior to Procedure)		✓	
Procedure		✓		
Anesthesia Effectiveness*		✓		
Tube Placement Tolerability*		✓		
Suction Tolerability*		✓		
Post-Procedure Tolerability		✓		
Adverse Events		✓	✓	✓
Study Exit				✓

*Anesthesia effectiveness, cranial nerve physical exam and tolerability assessments for in-office subjects only.
** 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.
† If tube(s) have been confirmed to have extruded, no additional follow-up visits are required and the subject may exit prior to the 24 month visit.

12.0 ASSESSMENT OF SAFETY

12.1. 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. Adverse events will also include operative and recovery observation for lead-in procedures conducted in the OR with general anesthesia including, but not limited to, clinically-meaningful vital sign changes, emergence delirium, post-operative nausea, vomiting, disorientation, and complications related to intubation or induction.

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.

12.2. 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.

12.3. 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.

Health Canada Reporting

Investigational Drug AE Reporting:

The sponsor will notify Health Canada or any serious unexpected adverse drug reaction

- Where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information;
- Where it is fatal or life-threatening, within 7 days after becoming aware of the information.

Investigational Device AE Reporting:

The sponsor will notify Health Canada of any incident involving the investigational device that:

- Is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its the directions for use; and
- Has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were it to recur.

Preliminary Health Canada reporting timelines:
• Within 10 days after Sponsor becomes aware of an incident, if the incident has led to the death or a serious deterioration in the state of health of a patient, user or other person, or
• Within 30 days after the Sponsor becomes aware of an incident, if the incident has not led to the death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur.

12.4. Adverse Event Classification

Adverse Event Severity

Ear-related 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 5**).[66] Grade level of adverse event refers to the severity of the event. [redacted]

Table 5. Table of Ear-related Adverse Event Severity

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Ear pain	Mild pain	Moderate pain; limiting instrumental activities of daily living (ADL)	Severe pain; limiting self care ADL	-	-
External ear inflammation	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis; necrosis of soft tissue or bone	Urgent operative intervention indicated	Death
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Middle ear inflammation	Serous otitis	Serous otitis, medical intervention indicated	Mastoiditis; necrosis of canal soft tissue or bone	Life-threatening consequences; urgent intervention indicated	Death
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Ear - Other	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	

Table 6. Table of Other Events Adverse Event Severity

Adverse Event	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life Threatening)
Nausea/Vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2-3 loose stools or <400 gms/24 hours	4-5 stools or 400-800 gms/24 hours	6 or more watery stools or >800 gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Significant; prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Significant; prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	Significant; prevents daily activity
Illness or clinical adverse event	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Significant; prevents daily activity

Other adverse events (**Table 6**) will be classified as to the severity of the event based on the definitions consistent with AE severity grading scale provided by FDA Guidance (Sep 2007) entitled "Toxicity Grading Scale for healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials".[67] Grade level of adverse event refers to the severity of the 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 7**.

Table 7. 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[68]

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 8**.[69,70]

Table 8. 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

12.5. Safety Monitoring

Investigators will report all serious adverse events to the Sponsor within 24 hours of identification. The Sponsor and Medical Monitor(s) will promptly review information relevant to the safety of the device or drug. All serious and all unanticipated adverse device or drug-related events 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(s). The Medical Monitor(s) will review all AEs and their coding for accuracy and consistency periodically.

[redacted]

[redacted]

12.6. 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]

13.0 STATISTICAL METHODS

This pivotal study intends to evaluate effectiveness and safety of iontophoresis using the IPS and TDS for TT placement in-office for children indicated for tympanostomy tube placement (the pivotal cohort). The study also includes subjects enrolled into OR lead-in and in-office lead-in cohorts.

The pivotal phase of the study aims to confirm safety, and determine whether the in-office tube placement procedure achieves acceptable procedural success and tube placement tolerability rates. The pivotal cohort will consist of a sample of 222 children with evaluable data including 102 children age 5 to 12 years old, and 120 children less than 5 years of age. There are two primary endpoints for the pivotal cohort: (1) Procedural Success will be the proportion of subjects with Tusker Medical tympanostomy tubes placed in all indicated ears in an office procedure, and (2) Tube Placement Tolerability will be the mean subject-reported pain score following TDS tube placement using the Faces Pain Scale-Revised

(FPS-R) (children ages 5 and older only). The statistical tests for the co-primary endpoints are hypothesis tests against performance goals. Further details regarding the statistical methods may be found in the Statistical Analysis Plan CPR007004 which includes an appended Adaptive Design Report describing the primary endpoint statistical model and operating characteristics.

13.1. 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 Statistical package (3.2.1 or higher) will be used to perform all statistical analyses.

13.2. Analysis Sets

13.2.1. Full Analysis Set

All subjects in whom the lidocaine is introduced into the ear canal and for whom iontophoresis was initiated will be included in the FAS.

13.2.2. Per Protocol Set

The Per Protocol Set is a subset of the FAS and includes all 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).

13.2.3. Safety Analysis Set

The Safety Analysis Set will include all pivotal cohort subjects in whom the lidocaine solution is introduced into the ear canal.

13.3. Primary Endpoint Analysis

Procedural Success: The proportion of subjects in the pivotal cohort FAS achieving procedural success will be evaluated against a performance goal of 68%. The study design employs a Bayesian hierarchical gatekeeper strategy whereby the test against the performance goal occurs in two steps:

1) The initial test against the performance goal is conducted on the older children in the pivotal cohort, once the study has accrued evaluable data for 102 children ages 5 through 12 years of age.

   The primary hypothesis is

Test 1:

$$H_o: p_{5+} \leq 68\%$$
vs.
$$H_a: p_{5+} > 68\%$$

Where p_{5+} is the proportion of subjects 5 through 12 years old achieving procedural success.

This hypothesis will be tested using a Bayesian hierarchical model evaluating whether the posterior probability of H_a is at least 0.975, which is analogous to a classical hypothesis test at the 0.025 significance level in the FAS comprising only subjects 5 through 12 years old. This Bayesian analysis applies the test to the older group, while borrowing data from all enrolled evaluable subjects less than 5 years old, as appropriate given the performance results at the time of the first test. [redacted] If the older group achieves the performance goal, the second test is applied to the younger subjects as described in step 2. [redacted]

2) The final test for the procedural success primary endpoint is applied once the full pivotal cohort is enrolled (102 older subjects in Test 1, plus 120 younger subjects ages 6 months to less than 5 years old). The second test evaluates the younger subjects against the performance goal while borrowing data from the 102 older subjects using a Bayesian hierarchical model as appropriate given the performance of the older group.

Test 2:

$$H_o: p_{<5} \leq 68\%$$
vs.
$$H_a: p_{<5} > 68\%$$

Where $p_{<5}$ is the proportion of subjects in the younger group (6 months through <5 years old) achieving procedural success.

Test 2 is also performed using a Bayesian hierarchical model, requiring a 97.5% posterior probability of H_a. [redacted]

Tube Placement Tolerability: Mean subject-reported pain score following TDS tube placement using the Faces Pain Scale-Revised (FPS-R). The mean pain score for

subjects in the pivotal cohort FAS, for whom tube placement was successful, will be evaluated against a performance goal of 4.2 pain score.

The test against the performance goal is conducted on only the older children in the pivotal cohort, once the study has accrued evaluable data for 102 children ages 5 through 12 years of age.

The primary hypothesis is

$$H_o: \ p_{5+} \geq 4.2$$
$$\text{vs.}$$
$$H_a: p_{5+} < 4.2$$

Where p_{5+} is the mean Tube Placement FPS-R for subjects 5 through 12 years old.

This hypothesis will be tested using a standard classical t-test at the 0.025 significance level in the FAS comprising only subjects 5 through 12 years old. Tube Placement [redacted]

13.4. Secondary Efficacy Endpoint Analyses

Secondary endpoints will be tested on the 102 older children upon successful achievement of the primary endpoints. If the 102 older children pass the test, a gatekeeper design will be employed and the secondary endpoints will be tested on the full pivotal cohort once enrolled (102 older children plus 120 younger children). The secondary endpoints (Tube Patency, Tube Retention and Anesthesia Effectiveness) are functions of the tube and iontophoresis device performance and are not anticipated to vary by subject age. Therefore, testing the secondary endpoints on the full (pooled) pivotal cohort is appropriate.

13.4.1. TUBE PATENCY

Tube Patency is the proportion of subjects in the pivotal cohort FAS, in which a Tusker Medical tube was successfully placed, with functional tube patency in all successfully treated ears at the 3-week post-procedure follow-up visit.

The statistical test for the pivotal cohort Tube Patency secondary endpoint is a hypothesis test for the proportion of subjects with functional tube patency in all successfully treated ears at the 3-week follow-up visit against a tube patency performance goal. The mid-P[71,72,73] method for a single proportion will be used to test

$$H_o: p \leq 80\%$$
$$\text{Vs.}$$
$$H_a: p > 80\%.$$

This endpoint will be considered met if the p-value from the test is less than 0.025.

13.4.2. TUBE RETENTION

Tube Retention is the proportion of subjects in the pivotal cohort FAS, in which a Tusker Medical tube was successfully placed, with presence of a Tusker Medical tube across the tympanic membrane in all successfully treated ears at the 3-week post-procedure follow-up visit.

The statistical test for the pivotal cohort Tube Retention secondary endpoint is a hypothesis test for the proportion of subjects with a Tusker tube in all successfully treated ears at the 3-week follow-up visit against a Tube Retention performance goal. A mid-P method for a single proportion will be used to test

$$H_o: p \leq 88\%$$
Vs.
$$H_a: p > 88\%.$$

This endpoint will be considered met if the p-value from the test is less than 0.025.

13.4.3. ANESTHESIA EFFECTIVENESS

Anesthesia Effectiveness is the proportion of subjects in the pivotal cohort FAS, who completed iontophoresis for all indicated ears, with adequate anesthesia for tympanostomy tube placement in all treated ears as determined by physician's evaluation of TM anesthesia prior to tube placement.

The statistical test for the Anesthesia Effectiveness secondary endpoint is a hypothesis test for the proportion of subjects with adequate anesthesia for tube placement in all ears completing iontophoresis against an Anesthesia Effectiveness performance goal. The mid-P method for a single proportion will be used to test

$$H_o: p \leq 85\%$$
Vs.
$$H_a: p > 85\%.$$

This endpoint will be considered met if the p-value from the test is less than 0.025.

[redacted]

[redacted]

13.6. 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.

The study will present the totality of safety data, by subject including:

- Serious device, procedure, and drug-related events
- Other serious events
- Non-serious device, procedure, drug-related events
- Other non-serious events

These data will also be reported in the Lead-in OR and Lead-in Office cohorts. [redacted]

All AEs will be tabulated 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. 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. Duration and outcome of AEs will be reported in subject line listings.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13.8. Handling Drop Outs or Missing Data

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

Sensitivity analyses and handling of missing data is described in the Statistical Analysis Plan CPR007004.

[redacted]

[redacted]

[redacted]

14.0 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 and Assent 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 11.5.**

14.1. 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.

Example: 7001-JON-001

7001 = 4 digit Protocol Number

JON = Investigator Dr. Jones

001 = Number of subject enrolled

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

15.0 PREMATURE TERMINATION OR WITHDRAWAL

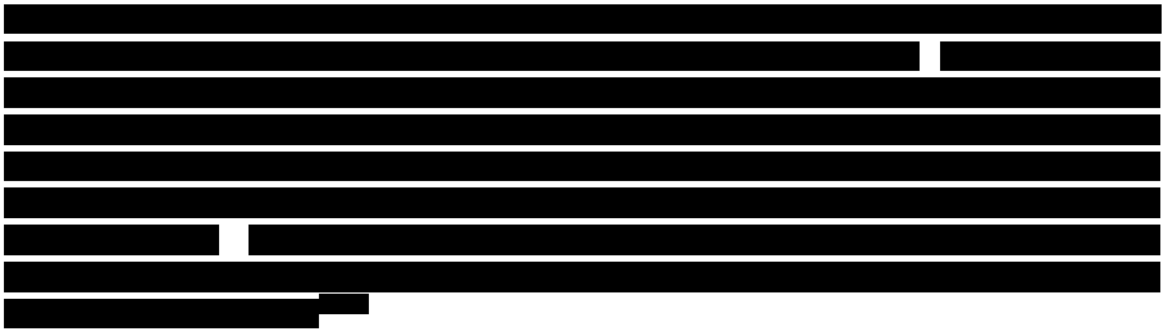
15.1. Subject Stopping Criteria

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 or subject's caregiver decides it is in the subject's best interest to withdraw
- Subject expresses intolerance or discomfort during the procedure and subject or subject's caregiver indicates they wish to stop the procedure and withdraw
- Investigator decides if a serious adverse event 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 a subject discontinues 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.

15.2. Study Stopping Criteria

The Sponsor or Investigator may terminate the study or center participation at any time for reasonable cause, and will provide sufficient notification.

Reasons for premature suspension of the trial include, but are not limited to:

- Risk to Subjects

- Lack of effectiveness [redacted]
- Inadequate enrollment
- Business reasons

Reasons for premature termination of an investigational site include, but are not limited to:

- Site is non-compliant to protocol, procedures or GCP
- Inadequate enrollment

Reasons for premature suspension of enrollment include but are not limited to:

- 3 serious Grade 3 or higher unexpected drug, device or procedure-related adverse events.

[redacted]

At the point the site or study is terminated, the site will immediately invoke all procedures required at the 3-week follow-up visit.

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

16.0 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 approximately 25 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.

17.0 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
Menlo Park, CA 94025

[redacted]

[redacted]

18.0 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.

19.0 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.

20.0 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.

21.0 DATA HANDLING AND RECORD KEEPING

21.1. 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.

21.2. 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.

21.3. 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.

22.0 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.

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