SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Lidocaine/Epinephrine Iontophoresis and Automated Tympanostomy Tube Insertion System
Device Trade Name:	Tula® System
Device Procode:	QJA
Applicant's Name and Address:	Tusker Medical 155 Jefferson Drive, Suite 200 Menlo Park, CA 94025 USA
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P190016
Date of FDA Notice of Approval:	November 25, 2019
Breakthrough Device:	Granted breakthrough device status (formerly known as the Expedited Access Pathway, or EAP) on February 14, 2019.

II. INDICATIONS FOR USE

Tula System: The Tula® System is intended to create a myringotomy and insert a tympanostomy tube using the Tula Tube Delivery System in pediatric (aged 6 months and older) and adult patients indicated to receive tympanostomy tubes. The Tula System is used to deliver a tympanostomy tube under local anesthesia induced using the Tula Iontophoresis System and TYMBION™, a combination of an amide local anesthetic and an alpha- and beta-adrenergic agonist.

TYMBION: TYMBION™, a combination of an amide local anesthetic and an alpha- and beta-adrenergic agonist, is indicated for the induction of local anesthesia of the tympanic membrane via iontophoresis using the Tula® Iontophoresis System in pediatric (aged 6 months and older) and adult patients undergoing tympanostomy tube placement using the Tula Tube Delivery System.

III. CONTRAINDICATIONS

The use of the Tula® System is contraindicated in the following patients:

- Cases in which the tympanic membrane is significantly atrophic, significantly retracted in the target location for tube delivery, or completely atelectatic.
- Patients presenting with tympanic membrane (TM) perforation(s). It is recommended that otoscopy and tympanometry be used in the assessment of the TM.
- Active or recent conditions of the tympanic membrane (eg, prior myringotomy with incomplete wound healing or re-epithelialization)
- Hemotympanum or other suspicion of aberrant vasculature (eg, carotid artery; high riding jugular bulb) impacting the tympanic membrane or middle ear.
- Patients presenting with lacerations/abrasions to the external auditory canal.
- Patients presenting with dimeric or monomeric tympanic membrane.
- Presence of otitis externa.
- Patients with electrically sensitive medical support systems (eg, pacemakers, defibrillators, cochlear implants).
- Patients with a history of sensitivity or allergic reaction to lidocaine hydrochloride (HCl), tetracaine, epinephrine, or any hypersensitivity to local anesthetics of the amide type, or any component of the anesthetic drug formulation.
- Patients with a familial history of insensitivity to lidocaine or other local anesthetics.
- Anatomy/visualization that necessitates tympanostomy tube placement in the posterior half of the tympanic membrane.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Tula System and the TYMBION labeling.

V. DEVICE DESCRIPTION

The Tula® System is a combination product that consists of an Iontophoresis System (IPS), a Tube Delivery System (TDS), and a lidocaine hydrochloride 2% and epinephrine 1:100,000 (0.01 mg/mL) otic iontophoretic drug solution (TYMBION) to be used with the IPS.

A. Iontophoresis System

The hand-held Iontophoresis Control unit (Control Unit) is a single-patient-use, battery-powered, non-sterile disposable medical device (**Figure 1**). It contains a microcontroller that is programmed to deliver a specific iontophoresis electrical current profile (ramp up, steady-state, ramp-down) which has a peak current of 0.8 mA. The Control Unit provides two independent channels of electrical current that share a single Return Electrode. The Control Unit includes embedded software that delivers a fixed amount of charge and informs the operator when charge delivery is complete.

The TYMBION drug product (see **B. TYMBION Drug**) is an ionic drug solution. When the Iontophoresis Control Unit is activated, the electrical current transports ions of lidocaine and

epinephrine into the tympanic membrane, thus greatly accelerating tissue uptake of the local anesthetic solution as compared to passive delivery. The amount of drug delivered to the tissue is directly proportional to the amount of charge supplied by the Iontophoresis Control Unit.[1] The total charge delivered in the iontophoresis cycle is not configurable or adjustable by the user, and the Control Unit cannot be reactivated once charge (drug) delivery is complete. The electrical charge delivery (and proportional drug delivery) is therefore a single fixed dose, which is identical for each ear treated.

The Control Unit can deliver current to a patient's left and right ears sequentially or simultaneously, if desired. The user interface of the Control Unit consists of two buttons, corresponding to the Blue and Yellow channels. The colors help identify the channels and either color connector may be used in the left or right ear. For each channel, a vertical array of three light emitting diode (LED) Progress Bars track the progress of the fixed electrical current delivery program. Each bar represents approximately one-third of the total time of the current delivery program, starting from the bottom bar to the top.

The Iontophoresis Earset and Earplug is shown in **Figure 2** inserted into a child's external ear canal. The Earplug provides a seal to keep the drug solution in the ear canal throughout the iontophoresis process and is available in six color-coded sizes to accommodate variation in patient anatomy. The Earset is connected to the Control Unit and contains the electrode that applies the electrical current to the TYMBION iontophoretic otic solution. The Earset and Earplug are single-use, disposable, non-sterile devices.

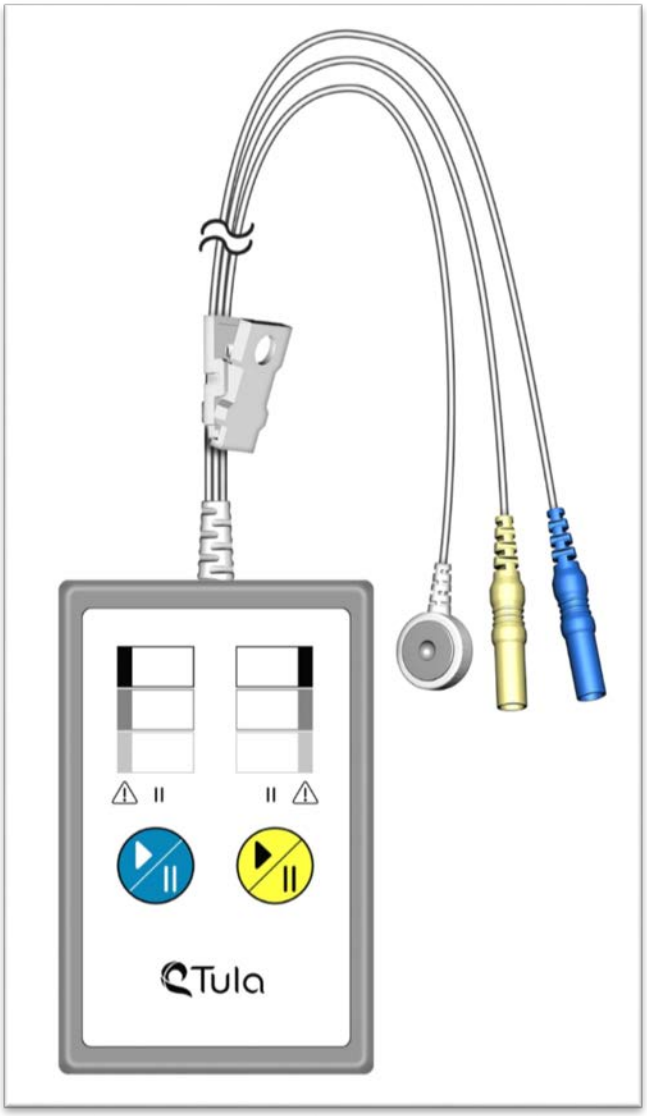


Figure 1: Iontophoresis Control Unit

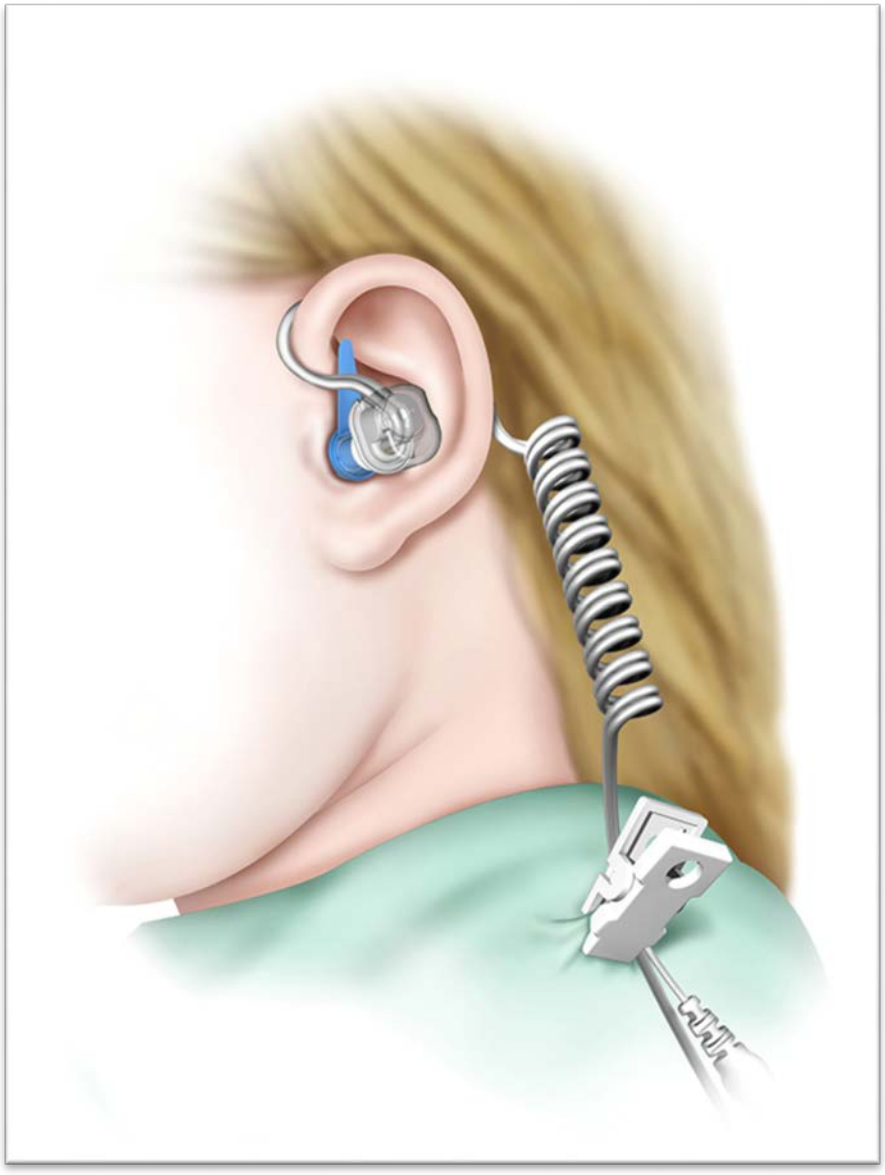


Figure 2: Inserted Earset/Earplug

B. TYMBION Drug Product Description

TYMBION is the proprietary name for lidocaine hydrochloride and epinephrine otic solution approved for the iontophoretic route of administration. TYMBION is a sterile, nonpyrogenic solution of lidocaine hydrochloride 2% (20 mg/mL) and epinephrine 1:100,000 (0.01 mg/mL) in water; provided in 20 mL, single-patient-use vials. TYMBION is the only lidocaine and epinephrine solution approved for use with the Tula® System, and the Tula IPS is the only iontophoresis system that should be used with TYMBION.

Lidocaine (**Figure 3**) is a local anesthetic of the amide type. The chemical name is lidocaine hydrochloride 2-(diethylamino)-2',6'-acetoxylidide mono-hydrochloride, monohydrate. It is a white crystalline powder freely soluble in water, with a molecular weight of 288.8 g/mol, and the molecular formula is $C_{14}H_{22}N_2O$•HCl •H_2O. Lidocaine stabilizes the neuronal membrane by inhibiting ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

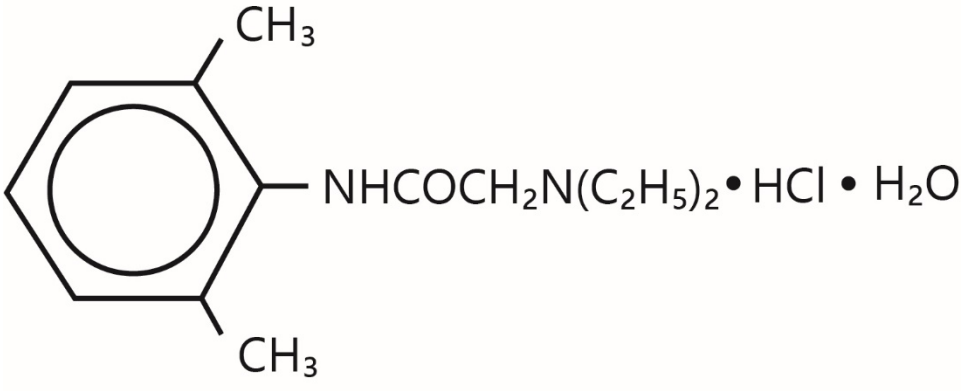


Figure 3: Structure of Lidocaine Hydrochloride

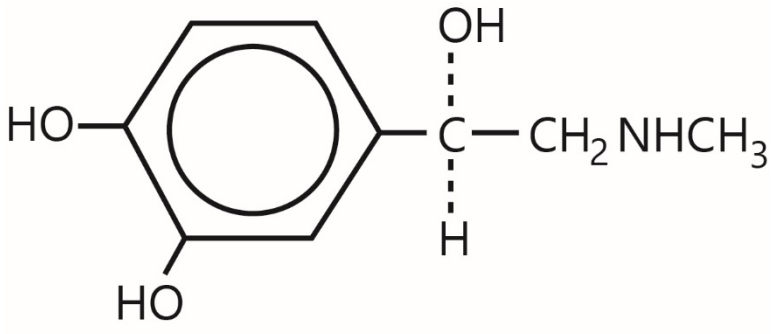


Figure 4: Structure of Epinephrine Bitartrate

Epinephrine (**Figure 4**) is a sympathomimetic (adrenergic) agent. Epinephrine bitartrate, designated chemically as L-3,4-dihydroxy-α-[(methylamino)methyl]benzyl alcohol bitartrate is a white, crystalline powder with a molecular weight of 333.29 g/mol. Its molecular formula is $C_9H_{13}NO_3$•$C_4H_6O_6$. Epinephrine contributes to the anesthetic effect due to its vasoconstrictor action, which decreases the rate of removal of lidocaine from the targeted tissue.

Inactive ingredients in TYMBION are sodium chloride, sodium metabisulfite, citric acid, and methylparaben. The solution may contain hydrochloric acid to adjust pH.

C. <u>Tube Delivery System (TDS)</u>

The TDS (**Figure 5**) is a device that deploys a preloaded tympanostomy tube (**Figure 6**) across the tympanic membrane with a single button-controlled activation. Upon activation by the user,

the device automatically creates the myringotomy and delivers the tympanostomy tube in a rapid fashion. The tube is delivered in less than 500 msec and the cutting element of the TDS is exposed only briefly upon actuation and is immediately retracted back into the device once the incision is made. The single-button automation, speed of the device, and very limited sharps exposure time are critical safety features when deploying tubes in awake, un-sedated pediatric patients. The tympanostomy tube has an inner lumen diameter of 1.14 mm and is made from silicone. The TDS is a sterile single-use device.

Figure 5: Tube Delivery Device

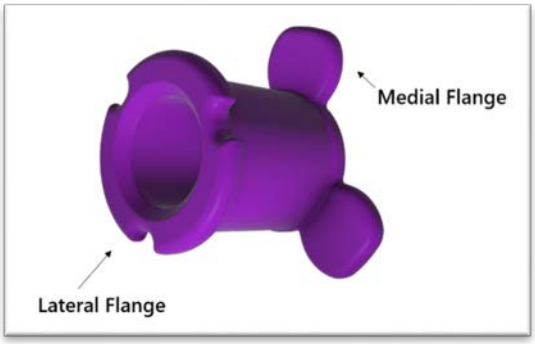


Figure 6: Tympanostomy Tube

D. Principles of Operation

The Earset Sizer is used to choose the proper size Earplug. The Earplug is affixed to the Earset, which is then inserted into the external ear canal of the patient, as shown in **Figure 2**. Earsets may be inserted bilaterally if treatment is intended for both ears. The Return Electrode is affixed to the patient's back or shoulder to complete the electrical circuit. After Earset insertion, a syringe with warmed TYMBION drug is attached to the Earset and drug is administered into the external ear canal of the subject until the Earset reservoir is filled, which is directly observed by the surgeon. The ear canal volume generally varies with age, but the ear canal volume can range from approximately 0.4mL to 1.0mL. The Earplug or Earset may be removed or fall from the ear canal while the procedure is going on when a patient moves or inadvertently grabs or pulls the Earplug or Earset. In such instances, the Control Unit detects the open circuit, immediately

discontinues electrical current, and enters an alert state. Once the Earplug is replaced, the Control Unit may be resumed by the physician and the Control Unit internally tracks the delivered charge (dose) to ensure proper overall charge/dosage delivery, despite the interruption.

The surgeon then activates the IPS, which applies a low level of direct current to the ionic drug solution, thus accelerating tissue uptake of the drug. Iontophoresis may be performed unilaterally or bilaterally as clinically indicated, and bilateral iontophoresis may be performed simultaneously in both ears. The iontophoresis process runs automatically and continuously tracks the applied charge and thus the anesthetic dose delivered. The nominal iontophoresis cycle takes 10 minutes to complete but could be lengthened if the surgeon pauses delivery or reduces the output current. Once the iontophoresis process concludes, the Earset is removed and drug is evacuated from the ear canal by tilting the head or wicking with cotton. The surgeon confirms complete drug removal from the external ear canal via visualization of the ear canal and tympanic membrane prior to deploying the tube.

The patient is placed in the operating position (typically reclined or supine) and the surgeon confirms proper anesthesia by gently tapping the TM with an otologic instrument. Once anesthesia is confirmed, the TDS is placed against the TM and activated by single button-push, thus rapidly and automatically delivering the tube across the TM. The contralateral tube is then inserted, if clinically indicated.

The TDS may be used in the Operating Room with general anesthesia, if desired (i.e., without concomitant use of the Iontophoresis System or TYMBION). Surgeons can then skip to Step 23 of the direction for use in Instructions for Use.

E. Packaging Configurations

The primary package required for the conduct of procedures is the Tula® System "Kit," which contains within it an Iontophoresis Control Unit, a Return Electrode, Earset(s) and Tube Delivery System(s), with the number of Earsets and TDS dependent upon the unilateral or bilateral nature of the Kit. Additional separate packages needed for a procedure include the Earplug Sizers and Earplugs, which are attached to Earsets after the proper size is chosen.

In addition to the device components of the Tula® System, a "Drug Pack" is required to complete the procedure (unless the procedure is performed in the Operating Room with general anesthesia). The Drug Pack contains a single vial of TYMBION drug packaged within a single TYMBION carton alongside two Syringes and two Syringe Caps.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives include the operating room placement of tympanostomy tubes under general anesthesia. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets their clinical needs and expectations.

VII. MARKETING HISTORY

The Tula® System has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE/DRUG ON HEALTH

Observed Adverse Events: The safety of TYMBION delivered via iontophoresis, using the Tula Iontophoresis System, was evaluated in four clinical trials, three with adult subjects (n=90) and one with pediatric subjects from 6 months to 12 years of age (n=269). All studies were conducted under FDA and IRB-approved protocols (IND123314 [two studies], G170002, G170193). Study 1, a prospective, multicenter study with adult subjects, and Study 2, a prospective, multicenter study with pediatric subjects, evaluated the safety of iontophoretically administered TYMBION in subjects undergoing tympanostomy tube placement. Safety was evaluated for up to three weeks in adult subjects and up to 12 months in pediatric subjects.

The most commonly reported drug-related adverse reactions (> 2% of subjects) to occur in Study 1 or Study 2 with TYMBION are described in Table 1. One of the adverse reactions of vertigo and dizziness observed in Study 1 was considered to be a vestibular symptom resulting from TYMBION inadvertently entering the middle ear.

Table 1. Drug-Related Adverse Events Occurring in > 2% of Treated Subjects

Adverse Reaction	Study CPR 007003, Group B (N=30)	Study CPR 007001 (N=269)
Inadequate anesthesia*	1 (3%)	12 (4%)
Vertigo / Dizziness	2 (7%)	-

* Inadequate anesthesia was defined as a response to the tympanic membrane tap assessment performed after TYMBION iontophoresis and prior to tympanostomy tube placement, which does not reflect the total number of subjects reported as failures on anesthesia effectiveness endpoint.

Potential Adverse Events: Potential adverse effects associated with the Tula® System are described below. Most potential adverse effects associated with the Tula® System are anticipated to be similar to those for any tympanostomy procedure.

- Tube occlusion, resulting in failure to perform intended purpose
- Infection could occur from airborne or water pathogens entering the middle ear
- Early extrusion of the tube
- Failure of the tube to self-extrude, requiring surgical intervention
- Dislocation of the tube into middle ear space
- Deployment of the tube into middle ear space
- Persistent or permanent perforations, requiring surgical intervention
- Tympanosclerosis
- Local or diffuse atrophy of tympanic membrane
- Patient allergy or sensitivity to silicone, resulting in tissue irritation
- Unintended TM perforation
- Blood in ear related to the myringotomy

- Recurring or persistent otorrhea
- Granuloma and/or cholesteatoma formation
- Temporary aural fullness
- Conductive hearing loss due to damage to middle ear structures
- Abrasion of the external auditory canal or meatus requiring treatment
- Erythema or burn at return electrode site
- Dizziness/vertigo during or after iontophoresis
- Temporary tongue numbness or taste disturbance
- Sensations of pressure or discomfort during the iontophoresis process
- Temporary appearance of small fluid-filled vesicles/blebs on the surface of the TM, and temporary sensation of muffled hearing
- Major bleeding due to contact with aberrant vasculature
- Allergic reaction to the anesthetic
- Swallowing of drug solution in the presence of an undetected tympanic membrane perforation, leading to high systemic exposure
- Inadequate anesthesia

For the specific adverse events that occurred in the clinical studies please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

The following nonclinical studies were performed for the Tula® System:

A. Biocompatibility Testing

Testing was conducted to demonstrate that the components of the Tula® System are biocompatible. Biocompatibility testing was conducted in accordance with EN ISO 10993-1, Biological Evaluation of Medical Devices and in accordance with FDA guidance document "Use of International Standard ISO 10993-1, Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process," dated June 16, 2016. Testing was performed according to FDA Good Laboratory Practices (GLP) regulations (21 CFR, Part 58). All studies had passing results, and are summarized in **Tables 2, 3, and 4.**

The IPS devices are classified as surface devices with a limited contact duration with external skin, and the TDS is classified as an external communicating device with limited tissue contact duration. The tympanostomy tube that is delivered by the TDS is an implant contacting tissue for greater than 30 days. Testing supporting the biocompatibility of the IPS and TDS/tube is found in **Tables 2 and 3**, respectively. In order to ensure that drug/device interactions do not leach chemicals that may present adverse biological effects, a chemical characterization study was completed (**Table 4)**.

Table 2: Summary of Biocompatibility Tests and Results for the IPS

Test	ISO Standard	Test Method	Result
Cytotoxicity	10993-5	MEM Elution	Pass

Irritation	10993-10	Intracutaneous Reactivity	Pass
Sensitization	10993-10	Maximization Sensitization	Pass

Table 3: Summary of Biocompatibility Tests and Results for the TDS and Tympanostomy Tube

Test	ISO Standard	Test Method	Result
Tests for both TDS and Tympanostomy Tube			
Cytotoxicity	10993-5	MEM Elution	Pass
Irritation	10993-10	Intracutaneous Reactivity	Pass
Sensitization	10993-10	Maximization Sensitization	Pass
Additional Tests for Tympanostomy Tube Material			
Acute Systemic Toxicity	10993-11	Systemic Injection	Pass
Genotoxicity	10993-3	Bacterial Reverse Mutation	Pass
Implantation	10993-6	Muscle Implantation	Pass

Table 4: Summary of Chemical Characterization Test from Drug/Device Interaction

Test	Standards	Test Method	Result
Chemical Characterization	10993-17 10993-18 10993-12 USP 1663	Exhaustive Extraction (Infrared, GC-MS, UPLC-MS, ICP-MS) Simulated Use (Infrared, GC-MS, UPLC-MS, ICP-MS)	Pass Pass

B. Electrical Safety

The IPS is a single-use battery-powered device that is designed to apply a low level of electrical current into the TYMBION solution present in the external ear canal of the patient, via an electrode in the Earset and the Return Patch. The device was tested in accordance with IEC60601-1 (General requirements for basic safety and essential performance) and IEC60601-1-2 (Electromagnetic compatibility) and met all applicable requirements.

C. In Vitro Testing

The TDS and IPS were tested to evaluate device performance after sterilization (TDS only), transit conditioning and simulated transportation to verify the devices perform as intended. **Table 5** describes the completed testing for the TDS and Tube. **Table 6** summarizes the testing associated with sound generation, and **Table 7** describes IPS testing. All testing met the acceptance criteria.

Table 5: Summary of Key Bench Testing, TDS and Tube

Test	Purpose	Acceptance Criteria
Tube deployment	To assess the ability of the TDS to properly deploy the tympanostomy tube.	TDS must deploy the tube into a qualified and clinically-relevant bench model.
Tube deployment time	To assess the speed of deployment.	The tube must be delivered in less than 500msec once the TDS is actuated.
Actuation Force	To demonstrate that the force required to press the TDS button is acceptable.	The button actuation force must be less than 9N.
Geometric Measurements	To verify that the components of the TDS and Tube are as specified in device drawings.	Device components must be as specified in device drawings.
Cutter Excursion	To ensure the cutter excursion from the device is controlled properly.	The cutter must travel less than 0.118 inches past the edge of the TDS.
Tip Radius	To verify that the tip of the TDS is properly atraumatic.	There must be at least a 0.002 inch radius on the tip of the TDS.
Joint strengths	To assess device joint strengths.	The device joints must be capable of withstanding anticipated clinical forces.

In addition, because the Tube Delivery System creates sound during actuation, Hearing Safety and Loudness Discomfort testing was performed for the Tube Delivery System. The acceptance criteria of 130 dB SPL for Hearing Safety is based on scientific literature[2], which is lower than the corresponding OSHA standard for Occupational Noise Exposure (29 CFR Part 1926.52(e)), which describes a maximum limit for exposure to impulsive or impact noise of 140 dB SPL. A calibrated microphone was placed 30 mm from the TDS and sound measurements in decibels, sound pressure level (dB SPL) were captured. Acceptance criteria for loudness discomfort level were based on scientific publications for brief duration impulse sounds[3,4]. All sound generation testing successfully met the acceptance criteria.

Table 6: Summary of Sound Generation Testing, TDS

Test	Purpose	Acceptance Criteria	Test Results
Hearing Safety	To confirm the sound generated by the TDS is not dangerous	Sound generated by the TDS must be limited to 130dB peak SPL.	Pass Mean=70.6 dB

Test	Purpose	Acceptance Criteria	Test Results
			Max = 79.6 dB
Hearing Comfort	To confirm the sound generated by the TDS is not uncomfortable.	Sound generated by the TDS must not exceed 100 dB SPL for durations longer than 300 msec. For durations shorter than 300 msec, a formula as per the scientific literature was used to calculate the allowable limit.	Pass Mean=70.6 dB Max = 79.6 dB

Table 7: Summary of Key Bench Testing, IPS

Test	Purpose	Acceptance Criteria
Return Electrode Electrical and Chemical Properties	To assess the ability of the Return Electrode to properly complete the iontophoresis circuit.	The Return Electrode must have a resistance of less than 3k Ω and a pH of 6.2.
Return Electrode Dimensions	To verify the dimensional properties of the Return Electrode.	The Return Electrode must be 1.75" x 2.25" and must contain a snap interface compatible with the IPS cabling
Earplug Adhesive Properties	To assess the tackiness of the adhesive on the Earplug which is used to secure the Earplug in the external ear canal.	The tack force must exceed 1.7N. The force required to remove the liner covering the adhesive must be less than 9.8N. The force required to remove the Earplug from the ear canal must be less than 5N.
Earplug Attach/Detach	To confirm the Earplug/Earset remain functional after several attachment and detachment cycles.	Functional requirements must be met after 4 attachment and 3 detachment cycles.
Earset and Control Unit Geometric Properties	To verify the geometric properties of the Earset and Control Unit components.	Earset and Control Unit components must be as specified in device drawings.
Electrical Resistance	To confirm electrical continuity between appropriate connections and no short-circuits.	The resistance between the electrode in the Earset and the Control Unit is no more than 5.0 Ω. The resistance between the left and right ear electrodes (open circuit) must exceed 10M Ω.
Charge Delivery, Accuracy, and Ramps.	To verify that the IPS is capable of reliably delivering the proper charge to the drug solution, and to verify that	Charge delivered must be 6.36mAmin ± 10%. Measured

Test	Purpose	Acceptance Criteria
	the device measuring capabilities are robust.	voltages must have an error no greater than 10%. The ramp-up and ramp-down phases of the iontophoresis program must be delivered as designed.
Leak and Burst Testing	To verify that the device joints and components interacting with the fluid pathway do not leak or burst.	The Earset fluid path components must not leak fluid or burst when exposed to clinically-anticipated forces.
Ear Canal Pressure Testing	To demonstrate that the pressure in the ear canal while filling with drug is tolerable and not dangerous, and to verify proper venting function of the Earset system.	Ear canal pressure must be less than 25 kPa.
IPS LED and Button Functionality Testing	To verify proper functionality of the device LED indicators and buttons.	The LEDs and buttons must pass all functional requirements.
IPS Current and Voltage Safety Detection	To verify that the IPS is capable of detecting scenarios of high voltage or high current delivery and properly transitions into a fault scenario to discontinue current delivery.	The IPS must be capable of detecting and reacting to an electrical current of greater than 0.89mA or a voltage of greater than 34V.
IPS Error and Fault Detection	To verify the IPS is capable of detecting electrical anomalies and properly reacting.	The IPS must be capable of detecting low electrode current, low battery, stuck button, POST failure, intermittent connectivity, open circuit conditions, unrecoverable faults and react properly.
IPS User Interface Testing	To verify the IPS capability to accept a user input to Pause the current delivery, to Reduce the current delivery, and to resume nominal current delivery.	The IPS must be capable of properly receiving and reacting to user input (button presses) to initiate a Pause or Reduce in current, and to resume Nominal current.
Multi-Use Control	To confirm that the IPS properly limits charge delivery to a single programmed dose.	The IPS firmware must prevent an attempt by the user to run the iontophoresis sequence a second time.
Cable Disconnect	To demonstrate that the connection between the Control Unit and the Earset cabling is robust.	The force to disconnect the cabling must exceed 1.4N.

D. Packaging Testing

Device packaging verification was performed to demonstrate that the Tula® System sterile barrier packaging can withstand anticipated distribution hazards (simulated as per ISO 2233 and ASTM D4169) and that sterility of the TDS is maintained through the labeled shelf life. Package integrity testing included visual assessment, seal measurements, bubble leak detection (as per ASTM F2096), and seal strength (as per ASTM F88). Testing confirmed that the packaging properly protects the components of the Tula® System and maintains sterility. Packaging testing for the TYMBION Drug Pack confirmed that the package protects the physical integrity of the TYMBION vial through simulated environmental and transit challenges.

E. Sterility (TDS)

The TDS is sterilized using ethylene oxide (EO) gas and has been validated according to ISO 11135, Sterilization of health care products- Ethylene oxide- Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices. Results demonstrate that the EO sterilization process provides a minimum Sterility Assurance Level (SAL) of 10^{-6} and residual levels of EO and ethylene chlorohydrin (ECH) were within acceptable ranges for limited exposure devices as specified in ISO 10993-7, Biological evaluation of medical devices- Part 7: Ethylene oxide sterilization residuals. In addition, the amount of bacterial endotoxin was verified to be within the specification limit of 10 EU/device.

F. Reprocessing (Earplug Sizer)

The Earplug Sizer is a non-sterile reusable device that contacts intact skin and is cleaned and disinfected after each use. Cleaning validation was successfully completed, ensuring protein levels of the soiled and cleaned Earplug Sizer was reduced to $\leq$ 6.4 µg/cm^2 and carbohydrate levels reduced to $\leq$ 1.8 µg/cm^2. Low level disinfection validation was successfully completed, demonstrating that intentionally contaminated devices achieved at least a 6 log bioburden reduction.

G. Shelf Life (Device and Drug)

Device functional testing and packaging system testing was conducted following aging to demonstrate that the device and packaging performed within specifications for the labeled shelf life. Assigned shelf life of TYMBION is supported by stability testing of the drug product for appearance, identity, sterility, degradants, and pH. Additional in-use stability testing was performed to demonstrate that TYMBION is stable when subjected to iontophoresis using the IPS.

Table 8: Shelf-life information for the Tula® System

Component	P190016 Claimed Shelf Life
Earset	6 months
Earplug	5 months
Control Unit	24 months

Component	P190016 Claimed Shelf Life
Return Electrode	4 months
Syringe	60 months
Syringe Cap	60 months
Earplug Sizer	N/A – reusable
Tube Delivery System	12 months
TYMBION Drug	18 months

H. Animal Studies

Two animal studies were conducted under GLP regulations to assess the ototoxic potential of TYMBION when administered via iontophoresis to the external ear canal and tympanic membrane.

The first study assessed the ototoxic potential of a single dose of TYMBION and included a total of 48 guinea pigs. Experimental groups included iontophoretic administration of TYMBION doses that exceed the nominal human dosage by a factor of at least 4X. Control groups included saline with or without 2x iontophoresis, drug vehicle, and positive control. Additionally, TYMBION was injected directly into the middle ear as a test for the scenario where TYMBION may be applied in the presence of an undetected tympanic membrane perforation.

Animals were followed for 28 days, and evaluations included clinical observations, neurological observations, otoscopy, wound healing assessments, auditory brainstem response, organ and body weights, macroscopic and microscopic histopathology, and cytocochleogram. The results support the otic safety of TYMBION when administered using the IPS as directed.

A second study was conducted to assess the ototoxic potential of repeat doses of TYMBION, administered over several days to simulate the scenario where a first procedure may not be successful, and a second procedure is conducted on a different day. A total of 62 guinea pigs were included in the repeat-dose study. The animals were exposed to iontophoretically administered TYMBION delivered on Day 1/Day 5 (Groups 1 and 2) or Day 1/Day 5/Day 10 (Group 3). On each dosing day, Groups 1 and 3 received at least the clinical dose and Group 2 received at least twice the clinical dose. Control groups included saline with or without 1x iontophoresis, drug vehicle, and positive controls.

Animals were followed for 28 days after administration of the final dose, and evaluations included clinical observations, neurological observations, otoscopy (erythema, edema, and tympanic membrane perforation scores), auditory brainstem response, organ and body weights, macroscopic and microscopic histopathology, and cytocochleogram. Results showed residual shifts in auditory brainstem response at 28 days after the final dose, likely related to external ear canal debris and inflammation. Treatment-related histological findings included minimal to mild epithelial cell hyperplasia and increased incidence of minimal to mild fibroplasia of the tympanic membrane. For all TYMBION dosage levels and intervals, there was no clear treatment-related adverse impact of the repeat dosing on ossicular structures, ossicular mobility, cochlear hair cells, or microscopic findings in the inner ear.

I. Chemistry, Manufacturing, and Controls (CMC) Testing

Release testing is performed on TYMBION drug, as summarized in **Table 9**.

Table 9: Analytical Release Testing

Test	Test Description
Appearance	A visual inspection is conducted to verify that TYMBION meets appearance specifications and is free of particulates.
Identity	Assays are conducted to verify the identity of the drug substances lidocaine and epinephrine.
Total Content	Assays are conducted to quantitatively verify that the total amount of lidocaine and epinephrine in TYMBION meets specifications.
Degradation Products / Impurities	Assays are conducted to quantitatively verify that the amount and type of degradation products and impurities meet specifications.
pH	pH testing is conducted to ensure that pH is within specifications.
Bacterial Endotoxins Test	The amount of bacterial endotoxins present is verified to be within specification limits.
Sterility	Verification that the requirement for labeling the drug as sterile has been met.
Inactive Ingredients	Assays are conducted to quantitatively verify the inactive ingredient concentrations meet specification.

X. SUMMARY OF PRIMARY CLINICAL TRIAL

Tusker Medical performed a clinical study, OTTER (in-**O**ffice **T**ympanostomy **T**ube plac**E**ment in child**R**en; NCT03323736), to establish a reasonable assurance of safety and effectiveness of the Tula® System for the placement of tympanostomy tubes in unsedated and unrestrained children in a physician office setting. The study was conducted under IDE G170193. Data from the study were the primary basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The OTTER study was a prospective, single-arm, multi-center, non-randomized study in pediatric subjects undergoing tympanostomy tube placement between November 2017 and February 2019. The database for this PMA included data collected through May 2019. There were 18 investigational sites.

The three cohorts in the study were as follows: Operating Room (OR) Lead-In Cohort, Office Lead-In Cohort, and Pivotal (as described by the applicant) Cohort. Each investigator was required to treat a minimum of two OR Lead-In subjects under general anesthesia using the TDS alone without iontophoresis. Following completion of the OR Lead-In procedures, each investigator was required to treat a minimum of two Office Lead-In subjects undergoing tympanostomy tube placement under local anesthesia using the TDS and IPS with TYMBION. Upon completion of the OR and Office Lead-In subjects, investigators were permitted to begin treating subjects in the Pivotal Cohort.

The Pivotal Cohort consisted of two age groups. The "younger pivotal cohort" included children 6 months to less than 5 years of age (i.e., have not yet had their 5th birthday) and the "older pivotal cohort" included children 5 to 12 years of age (i.e., have not yet had their 13th birthday). Both age groups were evaluated with a primary endpoint of Procedural Success. The 5 to12-year-old group was also evaluated with a second primary endpoint of Tube Placement Tolerability using the Faces Pain Scale – Revised (FPS-R) (refer to the Clinical Endpoints section for additional information). Distress was assessed in all subjects using the Faces, Legs, Activity, Cry, Consolability (FLACC) scale, a validated, video-based, observational method using an 11-point scale, 0 (no distress) to 10 (highest distress). During the procedure, subjects were video-recorded, and the videos were then transmitted to a core lab and scored by a psychologist with expertise in pediatric pain assessment. The Office Lead-in Cohort enrolled 47 subjects and the Pivotal Cohort enrolled a total of 222 subjects, with prospective power calculations requiring 120 evaluable children in the younger pivotal cohort and 102 children in the older pivotal cohort.

The Procedural Success endpoint was analyzed in a Bayesian hierarchical framework, with prospectively-designed borrowing of data between the younger and older pivotal cohorts, with the extent of borrowing dependent upon the similarity in results. The Tube Placement Tolerability endpoint was analyzed in a standard classical framework using a 1-sample t-test.

Medical Monitors, which included an otolaryngologist and a neuroscientist/audiologist, adjudicated adverse events, and a Clinical Events Committee (CEC) was formed to provide overall oversight for the study, including review of subject-reported pain scores. The CEC was comprised of a general otolaryngologist, a pediatric otolaryngologist, and a pediatric emergency room physician, with expertise in the assessment of pediatric pain. The CEC reviewed data from procedures for subjects who discontinued or had reported pain scores of four or greater on the FPS-R or FLACC, or who had a score of two or greater in the 'Legs' or 'Activity' category on the FLACC. They assessed whether the subjects with pain scores of four or greater represented a study-wide tolerability issue, safety risk, or unacceptable risk/benefit profile. They were also asked to evaluate any adverse events that were determined by the medical monitors to require additional medical review (refer to the Clinical Endpoints section for additional information). The CEC reviewed data and video with a frequency of every 50 subjects throughout the study who met the review criteria had the authority to modify or suspend the study.

Key Eligibility Criteria

Enrollment in the OTTER study was limited to subjects who met the following inclusion criteria:

1. Males or females at least 6 months old through 12 years of age at time of consent

2. Indication for tympanostomy tube insertion per Clinical Practice Guideline[5]

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

Subjects were not permitted to enroll in the OTTER study if they met any of the following 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 (e.g., 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 (e.g., history of inadequate anesthesia with dental numbing agents). (*not applicable to OR Lead-In subjects*)

12. Electrically sensitive medical support systems (e.g., 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.

Follow-Up Schedule

All subjects were scheduled for follow-up examinations at 3-weeks post- procedure. Although the long-term therapeutic benefit of the implanted tube itself was expected to be similar to other commercially available tympanostomy tubes and long-term clinical outcome assessments were not objectives of this study, subjects who had tympanostomy tubes present at 24 months underwent a final follow-up evaluation.

The primary endpoints were evaluated at the immediate conclusion of the procedure. The 3-week follow-up visit captured any residual adverse events and other potential safety issues. Additional follow-up beyond 3 weeks (6, 12, 18, 24 months) was included in the protocol to characterize tube retention, but was not required to establish the safety and effectiveness of the Tula® System. **Table 10** shows the schedule of evaluations.

Table 10: Schedule of Evaluations

Evaluation	**Screening**	**Procedure**	**3 Weeks (-/+ 7 days)**	**6, 12, 18, 24 months[3] (-/+ 28 days)**
Informed Consent	✓			
Medical History	✓			
Cranial Nerve Physical Exam[1]	✓	✓	✓	
Concomitant Medications	✓	✓	✓	✓

Inclusion/ Exclusion Criteria	✓	✓		
Otoscopy	✓ (within 28 days prior to Procedure[2])	✓	✓	✓
Tympanometry	✓ (within 28 days prior to Procedure[2])		✓	✓
Audiometry	✓ (within 28 days prior to Procedure[2])		✓	
Procedural Success Primary Endpoint		✓		
Anesthesia Effectiveness[1]		✓		
Tube Placement Tolerability Primary Endpoint[1,4]		✓		
Suction Tolerability[1,4]		✓		
Post-Procedure Tolerability[1,4]		✓		
Adverse Events		✓	✓	✓
Tube Patency Assessment			✓	✓
Tube Retention Assessment			✓	✓
Distress Assessment [5]		✓		
Parental Survey[1]			✓	
Study Exit				✓[6]

1 Anesthesia effectiveness, cranial nerve physical exam, tolerability assessments, and parental survey for in-office subjects only.
2 Otoscopic examination, tympanometry and audiometry are considered standard of care for this subject population. Data obtained from these assessments within 28 days prior to procedure may be included as screening assessments.
3 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.
4 Tolerability assessments completed for children ages 5-12 only
5 Distress assessment performed via FLACC by external core lab using procedure video recordings
6 Subjects enrolled under Protocol Rev C or without tube placement may exit after the 3-week follow-up visit.

Clinical Endpoints

Safety Endpoint:
The occurrence of adverse events by subject was the safety endpoint. Adverse events included significant changes from baseline in otoscopy, audiometry, tympanometry, and cranial nerve function as well as return electrode erythema. Adverse events were classified as either ear-related, hearing-related, or other.

Effectiveness Endpoints:

The primary effectiveness endpoint of Procedural Success applied to both age groups in the Pivotal Cohort. The second primary effectiveness endpoint, Tube Placement Tolerability, applied only to the older age group in the Pivotal Cohort.

Procedural Success was defined as the proportion of subjects with successful placement of Tusker Medical tympanostomy tubes in all indicated ears in a single office procedure. If a subject required bilateral tube placement, both ears must have had successful tube placement for the subject to have been considered a success for this endpoint. The study was designed to demonstrate that the procedural success was greater than the prespecified performance goal of 68%. The performance goal of 68% was established via a formal Patient (Parent) Preference Study, which enrolled 400 subjects and was conducted via a web-administered survey instrument. The study described the in-office and OR-based procedure options for the insertion of ear tubes and described a set of attributes associated with each location. Choice questions were then presented using a risk graphic with 100 figures and respondents were presented with a binary choice. They could choose the OR procedure with a fixed success rate of more than 99% or the in-office procedure with a lower success rate. The procedural success threshold was found to be 68%, the level at which the respondents were indifferent to having the procedure in the office or in the OR. These results indicated that parents would prefer the Tula in-office procedure over the alternative (OR-based tube placement under general anesthesia) if the Tula procedure had a success rate that exceeded 68%.

Each age group was tested separately, however, a prospectively designed Bayesian hierarchical model was implemented which enabled data borrowing between the groups, with the extent of borrowing dependent upon the similarity/dissimilarity in results. The Procedural Success endpoint would be successfully met if the lower bound of the 95% credible interval exceeded the performance goal of a 68% success rate.

Tube Placement Tolerability was defined as the mean subject-reported pain score following successful tube placement using the FPS-R. This endpoint was used for the older age group, children 5 to 12 years of age, because younger children are incapable of reliably completing self-reported pain scales. The study was powered to demonstrate that Tube Placement Tolerability was less than the performance goal of a mean score of 4.2 (on a pain scale of 0 to10). Success was declared if the upper bound of the 95% confidence interval was less than 4.2. The performance goal of 4.2 was based on an independent study in 620 children where the mean FPS-R score associated with “mild pain” was reported as 4.9, with a 95% Confidence Interval of 4.2 to 5.6.[6] Therefore, demonstrating that the discomfort associated with Tula tube placement was rated less than 4.2 on the FPS-R scale, would suggest that the mean discomfort associated with the Tula procedure was below the lower 95% confidence bound of the “mild pain” range.

Secondary effectiveness endpoints were as follows, and were tested using statistical methods that controlled for type I error and multiplicity:

- Tube Patency: 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 follow-up visit. The mid-P method with a significance level of 0.025 was used to test whether Tube Patency was greater than 80%. Functional patency

was determined through clinical assessments including otoscopic examination and tympanometry.

- Tube Retention: 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 mid-P method with a significance level of 0.025 was used to test whether Tube Retention was greater than 88%.
- Anesthesia Effectiveness: The proportion of subjects in the pivotal cohort who completed iontophoresis for all indicated ears, with adequate anesthesia for tube placement in all treated ears as determined by physician's evaluation of tympanic membrane anesthesia prior to tube placement. The mid-P method with a significance level of 0.025 was used to test whether Anesthesia Effectiveness was greater than 85%. Of note, all subjects who failed on this endpoint were reported as having inadequate anesthesia in the adverse event database.

Additional unpowered but prospectively-defined exploratory effectiveness assessments included the following:

- Procedural Tolerability (FLACC): Procedural videos were evaluated by a core lab under supervision of a pediatric psychologist with expertise in pediatric distress assessment using the FLACC scoring method.
- Post-Procedure Tolerability (5 to 12 year-old subjects only): The FPS-R instrument was used to assess the discomfort five minutes after the tubes were placed. Post-Procedure Tolerability data may provide useful information on the duration of discomfort, if any, associated with the procedure.
- Operating Room Procedural Success: If a subject has an unsuccessful in-office procedure with Tula, their parents/clinicians may elect to perform a subsequent tube placement procedure using traditional methods under general anesthesia in an operating room. Operating Room Procedural Success measures the proportion of pivotal cohort subjects with unsuccessful in-office tube placement who elect and have successful operating-room tube placement. This assessment will provide insight as to whether the Tula procedure, if unsuccessful, creates any impediment to a subsequent successful OR-based procedure under general anesthesia.
- Parent Survey: A structured parent/guardian survey was conducted by the investigational site at the 3-week follow-up to assess parental satisfaction with the Tula procedure.

B. Accountability of PMA Cohort

At the time of database lock, 370 subjects were enrolled in the PMA study. Five subjects withdrew prior to consent and 24 were screening failures. Overall, 68 subjects were treated in the OR Lead-In Cohort, 47 were treated in the Office Lead-In Cohort, and 222 were treated in the Pivotal Cohort (120 subjects in the younger age group and 102 in the older age group). A total of 269 subjects were treated with TYMBION iontophoresis and the TDS, and the 68 OR Lead-In subjects were treated with the TDS only, as described in **Figure 7**. An additional four subjects, included in the Safety Set, had TYMBION administered into the ear canal, but did not have iontophoresis activated.

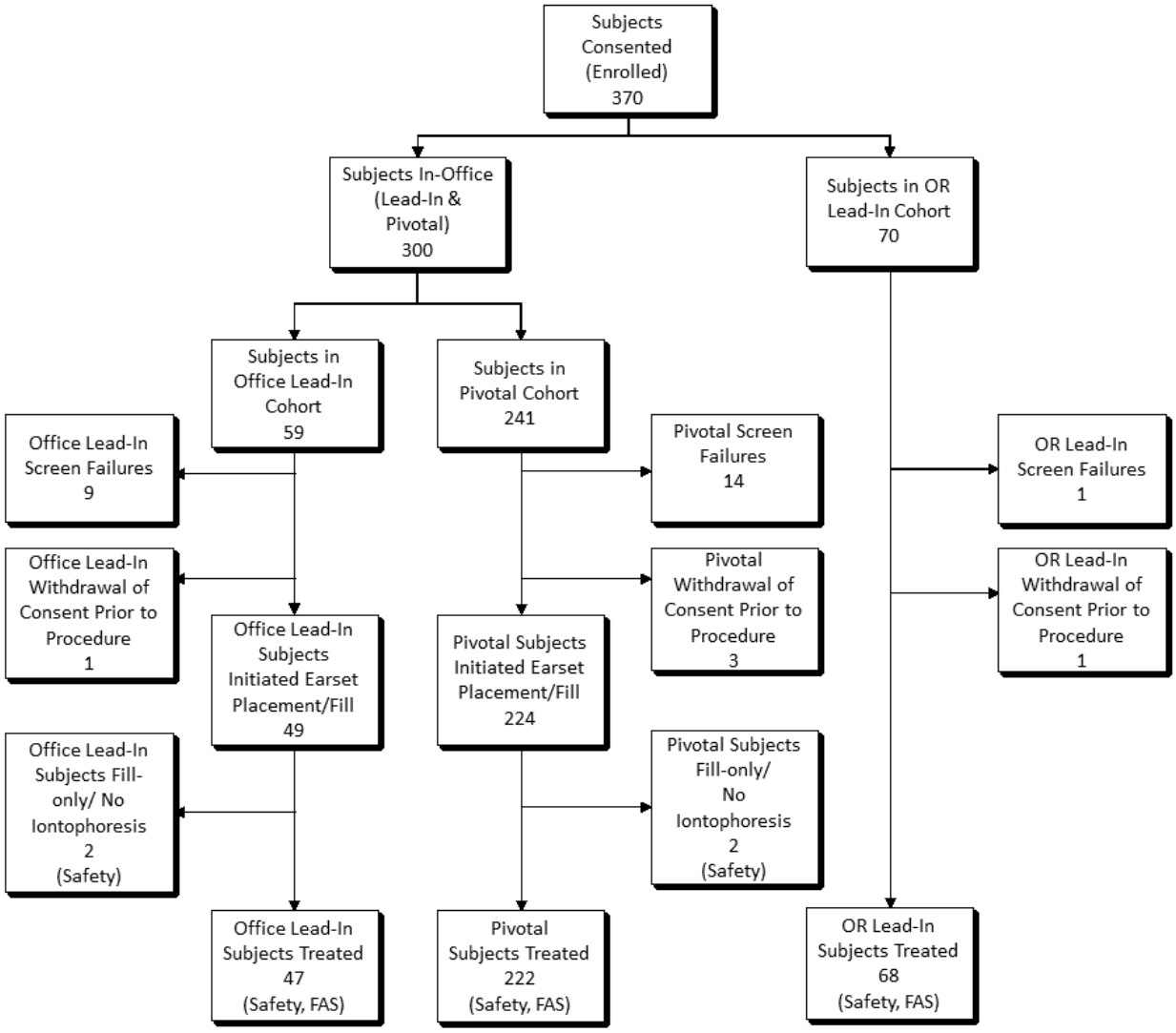


Figure 7: Subject Disposition

At the 3-week follow-up visit, subject availability was 68/68 (100%) for the OR Lead-In Cohort, 46/47 (97.9%) for the Office Lead-In Cohort, and 221/222 (98.6%) for the Pivotal Cohort.

C. Study Population Demographics and Baseline Parameters

The demographic characteristics of the study population were a reasonable representation of the demographic characteristics of the target patient population (refer to **Table 11**). Specifically, a larger number of children in the younger age group were evaluated compared to children in the older age group, which matches the age range most likely to require tympanostomy tube placement. Most children underwent bilateral tube placement, and a large number of children had a history of prior tympanostomy tube placement.

Table 11: Study Demographics (Safety Population*, SD refers to standard deviation)

	OR Lead-In N=68	Office Lead-In N=49	Pivotal <5 N=122	Pivotal 5-12 N=102
Age (years)				
Mean (SD)	3.4 (2.55)	4.7 (3.07)	2.3 (1.37)	7.6 (2.10)
Median	2.4	4.4	1.6	7.0
Min,Max	0.5, 11.3	0.5, 12.8	0.6,4.9	5.0,12.9
Sex				
Male	58.8% (40/68)	59.2% (29/49)	54.9% (67/122)	62.7% (64/102)
Female	41.2% (28/68)	40.8% (20/49)	45.1% (55/122)	37.3% (38/102)
Race				
White	77.9% (53/68)	75.5% (37/49)	88.5% (108/122)	75.5% (77/102)
Black or African American	8.8% (6/68)	12.2% (6/49)	5.7% (7/122)	16.7% (17/102)
Asian	4.4% (3/68)	0.0%	3.3% (4/122)	0.0%
Other	8.8% (6/68)	8.2% (4/49)	0.0%	6.9% (7/102)
None specified	0.0%	2.0% (1/49)	0.0%	0.0%
Asian and White	0.0%	2.0% (1/49)	0.0%	0.0%
Black or African American and White	0.0%	0.0%	2.5% (3/122)	1.0% (1/102)
Ethnicity				
Hispanic or Latino	20.6% (14/68)	12.2% (6/49)	9.0% (11/122)	19.6% (20/102)
Non-Hispanic or Latino	79.4% (54/68/)	85.7% (42/49)	91.0% (111/122)	80.4% (82/102)
Not specified	0.0%	2.0% (1/49)	0.0%	0.0%
Indicated Ears				
Unilateral	7.4% (5/68)	26.5% (13/49)	5.7% (7/122)	13.7% (12/102)
Bilateral	92.6% (63/68)	73.5% (36/49)	94.3% (115/122)	86.3% (88/102)

*Includes all OR patients, and all In-Office patients exposed to TYMBION with or without iontophoresis. There were 2 subjects in the Office Lead-In Cohort and 2 subjects in the Pivotal < 5 years Cohort who received TYMBION in the ear canal, but iontophoresis was not activated.

Additional baseline characteristics and past medical histories of a large number of treated subjects in all cohorts included acute otitis media, otitis media with effusion, and prior tube placement. On a per ear basis, 57.3% (75/131 ears), 67.1% (57/85 ears) and 61.4% (261/425 ears) had effusion at the time of procedure for the OR Lead-In, Office Lead-In and Pivotal cohorts, respectively.

D. Safety and Effectiveness Results

Safety Results

The analysis of safety was based on the occurrence of all adverse events by subject. There were no device, drug, or procedure-related serious adverse events in any OTTER subjects. The only adverse event that the investigators determined was related or potentially-related to the Tula

devices or drug that occurred at a rate greater than 2% was "inadequate anesthesia,"[1] which occurred at a rate of 4% (12/269 subjects that experienced iontophoresis of TYMBION[2]). These subjects were also included as failures on the secondary effectiveness endpoint of anesthesia effectiveness.

Audiometric testing was conducted at screening and again at the 3-week follow-up visit to evaluate hearing-related adverse events. A hearing impairment adverse event was prospectively defined to be a greater than 15dB worsening in air conduction pure tone average for either ear at the 3-week follow-up visit as compared to baseline. There were no hearing impairment adverse events detected in the study related to the Tula procedure or technology.

In addition to the Tula device or drug-related adverse events, additional adverse events related to the procedure were captured. All adverse events that were related or possibly related to the device, drug, or procedure are shown in **Table 12**.

Table 12. Adverse Events in the OTTER Study

Adverse Event	**OR Lead-In % (n/N)**[3]	**In-Office % (n/N)**
Inadequate Anesthesia	-	4.4% (12/269)
Occluded Tube	2.9% (2/68)	2.2% (6/269)
Ear Canal Abrasion	-	1.1% (3/269)
TM Perforation	1.5% (1/68)	0.4% (1/269)
Transient Medialized Tube	2.9% (2/68)	-
Otorrhea	1.5% (1/68)	-
Ear pain	-	0.7% (2/269)
Blood on TM	-	0.4% (1/269)
Medialized Tube	-	0.4% (1/269)
Otitis Externa	-	0.4% (1/269)
Partially Medialized Tube	-	0.4% (1/269)
Tympanosclerosis	-	0.4% (1/269)
Ear Bleeding	-	0.4% (1/269)
TM Inflammation	-	0.4% (1/269)
Ear Pressure	-	0.4% (1/269)
Oversized Myringotomy	-	0.4% (1/269)
Erythema at Return Electrode	-	0.4% (1/269)
Pain at Return Electrode	-	0.4% (1/269)

[1] "Inadequate anesthesia" was a specifically defined event related to the secondary endpoint of "Anesthesia Effectiveness". Anesthesia Effectiveness was defined in the protocol as "the proportion of subjects in the pivotal cohort, 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 tympanostomy tube placement." Therefore, the adverse event of "inadequate anesthesia" was associated with instances in which the physician determined (via touching the TM) that anesthesia was not sufficient to proceed with the procedure, and was not related to FPS-R scores provided by the subjects.

[2] The rate of inadequate anesthesia is shown here specific to the OTTER study (12/269 OTTER subjects). The rate of inadequate anesthesia described in Section VIII (13/359) additionally includes all studies of TYMBION lidocaine iontophoresis.

[3] Where n= number of subjects experiencing the adverse event and N= total number of subjects in the cohort.

Adverse Event	OR Lead-In % (n/N)[3]	In-Office % (n/N)
Transient Tongue Numbness	-	0.4% (1/269)
Dermatographia	-	0.4% (1/269)

In addition to adverse events that the investigators determined were related or potentially related to the Tula devices, drug or procedure, additional adverse events were recorded that represent common sequelae of tympanostomy procedures in general. **Table 13** shows total adverse event rates for otorrhea and tube occlusion, which are common post-tympanostomy sequelae. Otorrhea and occlusion rates, reported in Table 12, are for the combined OTTER pivotal cohort captured in the first month after the procedure, and the denominator includes only those ears that received Tusker tubes.

Table 13: Common Tympanostomy Procedure Sequelae (within 1 month)

Adverse Event	Rate
Otorrhea	5% (20/384 ears)
Tube Occlusion	3% (11/384 ears)

The rate of suction post tube placement was 64.1% (84/131 ears), 12.3% (8/65 ears) and 7.6% (29/384 ears) for the OR Lead-In, Office Lead-In, and Pivotal cohorts, respectively.

Effectiveness Results

For the primary effectiveness endpoint of Procedural Success, the analysis was based on a total of 222 treated subjects in the Pivotal Cohort, 120 subjects in the younger age group and 102 subjects in the older age group. For the second primary effectiveness endpoint of Tube Placement Tolerability, the analysis was based on a total of 89 subjects in the older age group. Key effectiveness outcomes are presented in Tables 14 and 15.

Table 14: Procedural Success Primary Endpoint

	6 months to <5 years	5 years to 12 years	All subjects
Pivotal Cohort	86% (103/120) (95% CI: 0.81-0.92)	89% (91/102) (95% CI: 0.83-0.94)	87% (194/222)
Office Lead-In Cohort	19/27 (70%)	18/20 (90%)	37/47 (79%)
All Tula Subjects	122/147 (83%)	109/122 (89%)	231/269 (86%)

CI = Credible interval

As previously discussed, the procedural success rate was compared to the performance goal of 68% using a Bayesian Hierarchical model. The Bayesian posterior probability of superiority to the performance goal of 68% for the younger and older pivotal cohorts was 0.9999 and 0.9999, respectively, greater than the pre-specified threshold of 0.975, indicating that the success criteria was met for both age groups; however, the lower overall procedural success rate in the younger, Office Lead-In Cohort, suggests there is a learning curve associated with use of the Tula® System in unsedated, unrestrained pediatric subjects less than 5 years of age.

Table 15: Tube Placement Tolerability Second Primary Effectiveness Endpoint, Procedure Success (5-12 years)

	Pre-procedure	Tube Placement	5 min Post-Procedure
Pivotal Cohort			
Mean FPS-R Score (SD)	0.59 (1.46)	3.30 (3.39)	1.69 (2.43)
Median FPS-R Score	0.0	2.0	0.0
95% Confidence Interval		(2.6, 4.0)	
P-value		0.0072	
In-Office Lead-in			
Mean FPS-R Score (SD)	0.44 (1.89)	1.78 (2.65)	0.67 (1.19)
Median FPS-R Score	0.0	0.0	0.0
All Procedure Successes			
Mean FPS-R Score (SD)	0.57 (1.53)	3 (3.31)	1.51 (2.30)
Median FPS-R Score	0	2	0
95% Confidence Interval		(2.42, 3.67)	

The second primary effectiveness endpoint was a test of superiority to a performance goal of 4.2 for the mean FPS-R score during tube placement. The mean FPS-R score during tube placement was 3.30 (out of 10), with a corresponding p-value of 0.0072 and 95% confidence interval of 2.6-4.0. These results met the pre-specified threshold of 0.025, indicating that the second primary effectiveness endpoint was met. To test the sensitivity of the conclusion, the analysis was repeated with the Office Lead-In Cohort included. Differences between the Lead-In and Pivotal Cohorts suggests the need for additional training. Since the results for the lead-in cohort were consistent with those of the pivotal cohort, additional training is not indicated by this analysis.

The mean and median pain scores for the procedural failures are described in Table 16. As would be expected, subjects who were not able to complete the procedure reported much higher pain scores on average, compared to the procedural successes. These differences were apparent 5 mins post-procedure.

Table 16: Tube Placement Tolerability Second Primary Effectiveness Endpoint, Procedure Failure

	Pre-procedure	Discontinuation Scores	5 min Post-Procedure
Procedure Failures	N=13	N=11	N=8
Mean FPS-R Score (SD)	1.08 (2.10)	6.4 (3.67)	3.5 (4.5)
Median FPS-R Score	0	8	1

Reasons for procedure failure are described in Table 17 for the pivotal cohort.

Table 17. Reasons for Procedure Failure with TYMBION (Study 2)

Reason for Procedure Failure	Pivotal Cohort, N (%)
Patient behavior	5% (11/222)
Inadequate anesthesia	3% (7/222)
Discomfort / anxiety	2% (4/222)
Anatomic challenges	1% (3/222)

Iontophoresis Intolerability	1% (2/222)
Partially Medialized Tube	0.5% (1/222)

Secondary effectiveness endpoint results are shown in Table 18. The results for these endpoints were first calculated in the older age group, 5 to12-year-old, Pivotal Cohort, and if successful, calculated in the pooled Pivotal Cohort. Prescribed sequential testing was also required to control for multiplicity. Statistical tests are conducted on the by-subject data, and the by-ear data is also provided in Table 18. All secondary endpoints met pre-specified success criteria.

Table 18: Secondary Endpoints

	Result	**Pre-Specified Criteria**	**p-value**
Tube Patency			
(3 weeks, by subject, 5-12 pivotal cohort)	90.7% (88/97 subjects)	> 80% (by subject)	p=0.0048
(3 weeks, by subject, pooled pivotal)	91.8% (191/208 subjects)	> 80% (by subject)	p<0.0001
(3 weeks, by ear, pooled pivotal)	95.0% (361/380 ears)		
(3 weeks, by subject, pooled office lead-in)	89.7% (35/39 subjects)		
(3 weeks, by subject, all Tula subjects)	91.5% (226/247 subjects)		
Tube Retention			
(3 weeks, by subject, 5-12 pivotal cohort)	99.0% (96/97 subjects)	> 88% (by subject)	p<0.0001
(3 weeks, by subject, pooled pivotal)	99.0% (206/208 subjects)	> 88% (by subject)	p<0.0001
(3 weeks, by ear, pooled pivotal)	99.5% (380/382 ears)		
(3 weeks, by subject, pooled office lead-in)	100% (39/39 subjects)		
(3 weeks, by subject, all Tula subjects)	99.2% (245/247 subjects)		
*Anesthesia Effectiveness**			
(by subject, 5-12 pivotal cohort)	94.1% (95/101 subjects)	> 85% (by subject)	p=0.0056
(by subject, pooled pivotal)	93.6% (206/220 subjects)	> 85% (by subject)	p<0.0001
(by ear, pooled pivotal)	96.4% (406/421 ears)		
(by subject, pooled office lead-in)	82.3% (39/47 subjects)		
(by subject, all Tula subjects)	91.7% (245/267 subjects)		

Additional exploratory analyses were conducted as per the protocol. Tube Retention at 3 weeks as shown in Table 18 was pre-specified to be calculated in the pivotal cohort only. However, additional Tube Retention data is available for OR and In-Office Lead-In cohorts and for a time period of 6 months in some subjects. Table 19 reports on supplemental Tube Retention data that includes all subjects with implanted tubes.

Table 19: Supplemental Tube Retention, All Cohorts

	Result
Tube Retention (6 months, by placed tube)	91.8% (314/342 tubes)

Videos of in-office procedures were collected and analyzed by a core lab led by a pediatric psychologist with special expertise in assessment of pediatric distress related to medical

procedures. The videos were scored using the FLACC method, a validated pediatric distress instrument. Table 20 summarizes the FLACC scores by procedural phase for successful procedures in the Pivotal Cohort subjects. FLACC scores are out of total maximum score of 10.

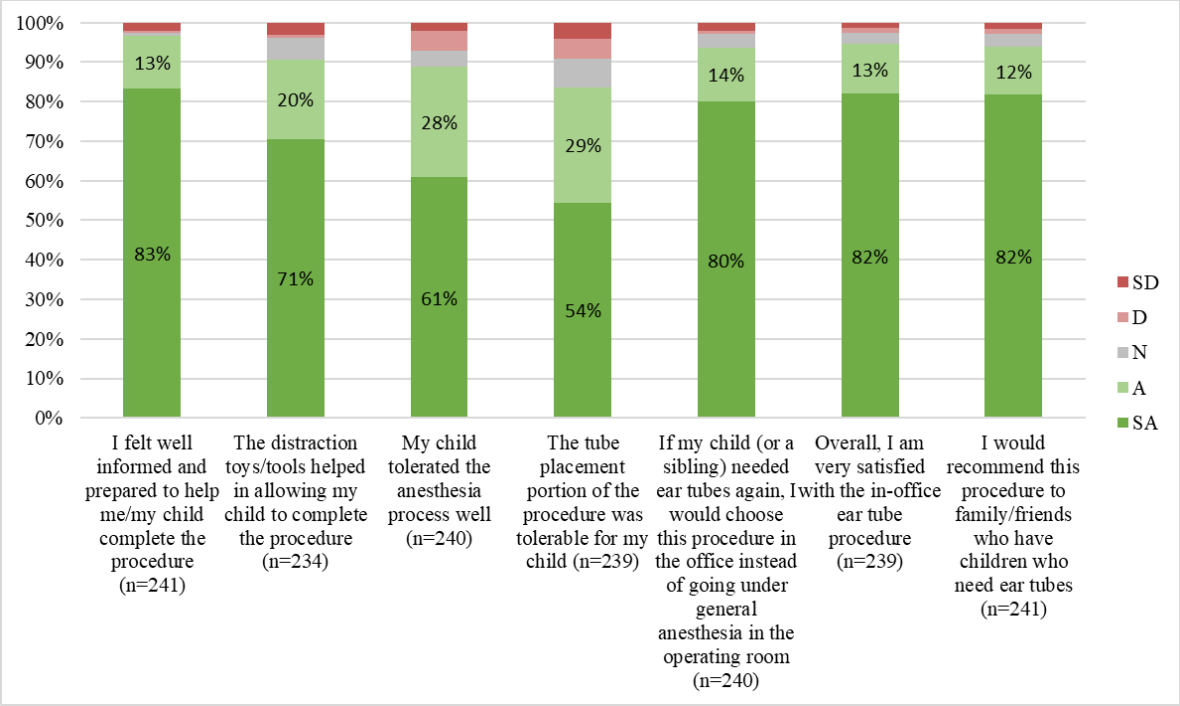
Table 20: FLACC Scoring

	Pre-Procedure Otoscopy	**Earset Installation and Drug Fill**	**Iontophoresis**	**Test for anesthesia and tube placement**	**Post-Procedure**	**Overall Procedure**
FLACC mean (SD), all ages	0.4 (1.5)	0.8 (2.2)	0.5 (1.6)	2.4 (3.3)	0.8 (1.7)	1.3 (2.6)
FLACC mean (SD), 6mo-4yr	0.7 (2.0)	1.4 (2.8)	0.8 (2.1)	4.0 (3.6)	1.3 (2.1)	2.3 (3.2)
FLACC mean (SD), 5yr-12yr	0.1 (0.7)	0.1 (0.5)	0.0 (0.1)	0.4 (1.2)	0.2 (0.9)	0.1 (0.8)

For procedural failures, the parent and ENT surgeon together decided whether to schedule a subsequent procedure using traditional techniques in the operating room. To determine if an unsuccessful Tula procedure was in any way an impediment to a subsequent successful OR procedure, the technical success rates of subsequent OR procedures were collected. Success in the OR was defined as the placement of tympanostomy tubes in all indicated ears. There was a 100% success rate (19/19 subjects) for OR procedures conducted subsequent to an unsuccessful in-office procedure. Note that not all parents selected OR-based tympanostomy tube placement if the in-office procedure failed. Additionally, for some subjects in which bilateral tube placement was indicated but only a single, unilateral tube was placed, the clinician and parent chose to delay an OR procedure pending an assessment of the clinical outcome of the unilateral tube.

During the 3-week post-procedure follow-up visit, parents completed a procedure satisfaction survey. Figure 8 shows the results from this survey, demonstrating a high level of satisfaction with the procedure.

Figure 8: Parent Satisfaction Survey Results (Office Cohorts)



SA=Strongly Agree, A=Agree, N=Neutral, D=Disagree, SD=Strongly Disagree

Additionally, for 77% (187/243) of office subjects, parents indicated that their child was capable of returning to normal activity immediately after the procedure was completed.

Subgroup Analysis

The study was not powered to detect any differences in outcomes by sex, but exploratory analyses were prospectively described. Sex differences in the primary effectiveness endpoints were examined using a chi-square test at the 10% significance level. There were no significant differences in Procedural Success or Tube Placement Tolerability by sex (p=0.22 and p=0.76, respectively).

The IPS has a feature, described as the Reduce feature, which allows the user to lower the device electrical current output by 25%. The Reduce feature can be activated if the subject complains of discomfort, tingling, or pressure sensations in the ear or at the site of the return electrode patch. When Reduce is activated, the IPS tracks the total charge delivered and lengthens the iontophoresis time accordingly, to ensure the targeted electrical (and therefore, drug) dose is delivered. While it was hypothesized that the use of the Reduce feature would not have an effect on the observed anesthetic effectiveness, prospectively planned analyses were conducted to evaluate subject-reported FPS-R Tube Placement Tolerability scores and use of the Reduce feature. **Table 21** shows the results (the mean pain score and standard deviation) of the Reduce subgroup analysis for the 5-12 Pivotal Cohort (as younger children do not have the FPS-R endpoint).

Table 21: Activation of Reduce Feature, Subgroup Analysis

	With Reduce (N=31)	Without Reduce (N=58)
Mean FPS-R Score (SD)	3.55 (3.13)	3.17 (3.53)

A chi-squared test resulted in a p-value of 0.5935, indicating that there is no relationship between the mean Tube Placement Tolerability FPS-R score and the use of the Reduce feature.

Pediatric Extrapolation

The OTTER study was conducted in a pediatric population, aged 6 months through 12 years of age. An additional study was conducted in 30 adults (IDE G170002). Extrapolation of safety and effectiveness data is required for children > 12 years of age through < 18 years of age.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 18 investigators of which none were full-time or part-time employees of the sponsor and 1 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 investigators
- Significant payment of other sorts: 0 investigators
- Proprietary interest in the product tested held by the investigator: 0 investigators
- Significant equity interest held by investigator in sponsor of covered study: 1 investigator

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A clinical evaluation in adult subjects, described below, was required prior to initiating studies in pediatric subjects to inform the safety profile of the IPS device and TYMBION, as well as the expectation of pain associated with tube placement using the Tula® system. Additionally, vital sign data captured during the adult study informed the decision of whether it was safe to proceed without such monitoring during the pediatric study.

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

The ADEPT study (IDE G170002) included adult subjects in two independent Groups (A and B), with the following objectives for each Group:

> Group A – to determine if active lidocaine iontophoresis is superior to sham lidocaine iontophoresis in providing anesthesia to the tympanic membrane for healthy adult volunteers
>
> Group B – to evaluate tolerability and safety of tympanostomy tube placement in adults indicated for tube placement following local anesthesia in a physician's clinic setting

Group A was a randomized, double-blind, sham-controlled design consisting of 40 healthy adult volunteers enrolled at two centers in the US. Subjects were randomized 1:1 to receive unilateral treatment either with active TYMBION iontophoresis or TYMBION with sham iontophoresis. The sham treatment arm received TYMBION in the external ear canal, but iontophoresis was not activated (i.e., passive delivery of drug). After completion of iontophoresis, tympanic membrane anesthesia was assessed using a dull otologic probe, and subjects rated the discomfort using the 100 mm Visual Analogue Scale (VAS). Both the subjects and investigators were blinded to treatment assignment.

Results indicated that active TYMBION iontophoresis (19 subjects) was shown to be superior to sham TYMBION iontophoresis (21 subjects) for effective anesthesia when analyzing subject-reported VAS pain scores, achieving the primary endpoint ($p=0.0097$).

Group B was a single-arm study consisting of 30 adults who required unilateral or bilateral tube placement, treated at eight centers in the US. Group B subjects received active iontophoresis using TYMBION for all ears that required tubes. Tubes were placed using the TDS, and pain scores were collected using both the VAS and the FPS-R, to provide insight into the correlation between the VAS and FPS-R scales. Vital signs were monitored pre-procedure and at intervals up to one hour following iontophoresis. The primary effectiveness endpoint for Group B was subject-reported pain scores following TDS tube placement compared to a performance goal.

Iontophoresis was completed in 30 subjects (38 ears). In one subject, tube placement was not attempted as the anesthesia was determined to be inadequate, which was detected during TM tap assessment post-iontophoresis. In the remaining 29 subjects (37 ears), tubes were successfully implanted in all indicated ears.

The mean VAS upon tube insertion was 9.4 mm and the median VAS was 3.0 mm. For bilateral ear procedures, the highest score was used in the effectiveness evaluation. The upper bound of a bootstrapped 95% confidence interval was 14.35 mm, meeting the primary effectiveness endpoint, which required the upper bound to be below 45 mm. The mean FPS-R for tube placement, by ear, was 1.2 (out of 10), whereas the mean VAS for tube placement, by ear, was 8.8 mm (out of 100 mm), with a Spearman correlation coefficient (FPS-R vs VAS) of 0.8418. All subjects (29/29) answered "Yes" to the question, "Did the local anesthetic provide adequate pain relief for the tube placement procedure?"

The ADEPT Group B results confirm that there is a reasonable assurance of safety and effectiveness when the Tula® System is used in adult subjects.

Pharmacokinetics

A pharmacokinetic study was completed under the Investigational New Drug program (IND123314) to evaluate plasma lidocaine and epinephrine concentrations in healthy adults, 18-50 years of age, before and after bilateral iontophoresis of either TYMBION otic solution or a 2% lidocaine solution (without epinephrine) to the tympanic membrane using the IPS.

The study was a randomized, double blind (Investigators and subjects), two-arm, prospective evaluation in adult healthy volunteers. Twenty-five (25) treated subjects were randomized 3:2 to either TYMBION iontophoresis or 2% lidocaine iontophoresis. Blood samples were collected from all randomized subjects for analysis of plasma drug levels using validated LC-MS-MS methods. Blood samples were collected prior to iontophoresis, immediately post iontophoresis, and at 5, 15, 25, 35, 50, 80, 110, 170 and 230 minutes post iontophoresis.

The lidocaine pharmacokinetic analysis characterized the plasma lidocaine concentration-time curve resulting after the administration of TYMBION or 2% lidocaine. No statistical difference in the geometric means of either lidocaine C_{max} or $AUC_{0\text{-}last}$ was shown when comparing the treatment formulation to that of the comparator (C_{max} 2.25 and 1.98 ng/mL, and $AUC_{0\text{-}last}$ 338 and 329 min*ng/mL, respectively). Measured plasma lidocaine concentrations for both TYMBION and 2% lidocaine arms were lower than the reported plasma levels, above 6 mcg free base per mL, at which objective adverse manifestations become increasingly apparent.

The epinephrine pharmacokinetic analysis compared plasma levels of epinephrine after iontophoresis of TYMBION to that of the comparator 2% lidocaine solution, which did not contain any epinephrine. The mean plasma epinephrine concentration values fluctuated between 23.1 to 30.8 pg/mL after administration of TYMBION, compared to 20.5 to 38.1 pg/mL after administration of the comparator formulation that did not contain epinephrine. No statistical difference in the geometric means of either C_{max} or $AUC_{0\text{-}last}$ was observed when comparing the treatment to that of the comparator (endogenous only) formulations (C_{max} 39.9 and 43.6 pg/mL, and $AUC_{0\text{-}last}$ 5022 and 4474 min*pg/mL, respectively). Both formulations resulted in similar median and mean values for C_{max} and $AUC_{0\text{-}last}$. There was no clinically significant elevation of the circulating endogenous epinephrine hormone. Measured epinephrine concentrations for both TYMBION and the 2% lidocaine comparator arms were within the reported normal range for endogenous epinephrine (30-50 pg/mL).

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to an FDA advisory committee.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The Procedural Success rate in children ages 6 months to < 5-years-old was 86% (103/120; 95% credible interval of 80-91%) and the Procedural Success rate in children ages 5 to 12 years-old was 89% (91/102; 95% credible interval of 82-93%), meeting the Performance Goal of 68% for both groups (Bayesian posterior probabilities of 0.9999 and 0.9999, respectively).

The mean Tube Placement Tolerability FPS-R score for 5 to 12-year-old subjects was 3.3, meeting the Performance Goal of less than 4.2 (p=0.0072). Although it can be challenging to compare the FPS-R scores reported for subjects undergoing tube placement in the OTTER study to FPS-R scores reported for other common pediatric interventions, it is worth mentioning that the mean FPS-R scores reported in the published literature do not appear to be clinically meaningfully different. Specifically, the mean FPS-R scores obtained in similarly aged patients receiving immunizations ranged from 3.0 to 6.6[7,8], dental injections from 3.0 to 6.3[9,10,11], IV cannulation 3.9[12], venipuncture from 3.3 to 6.5[13,14], and ear piercing 3.9[15]. The mean subject-reported FPS-R score obtained in the OTTER study five minutes after tube placement was 1.69, suggesting transient discomfort.

While mean Tube Placement Tolerability pain scores in the 6 months to 4-year-old subjects was not a primary efficacy endpoint, FLACC data for this population was reviewed. As summarized in Table 20, procedure discomfort was assessed for each phase of the procedure and overall. For patients who completed the procedure successfully, the phase of the procedure which involved the tympanic membrane tap and tube insertion had an average reported FLACC score of 4.0, out of a total possible score of 10.

The secondary effectiveness endpoints of Tube Patency (91.8%, p<0.0001), Tube Retention (99.0%, p<0.0001) and Anesthesia Effectiveness (93.6%, p<0.0001) were all met. Additional analyses demonstrate that Tube Retention was greater than 90% at 6 months for the ears with available 6-month follow-up data.

B. Safety Conclusions

The safety profile of the Tula® System to support approval of this PMA is based on the results of nonclinical studies, a pharmacokinetic study, the OTTER study, and the ADEPT study. The results from two nonclinical ototoxicity studies in guinea pigs support the otic safety of TYMBION, lidocaine hydrochloride 2% and epinephrine 1:100,000 (0.01mg/mL) otic iontophoretic solution when administered using the Tusker Medical Iontophoresis System. A clinical pharmacokinetic study demonstrated low systemic exposure to lidocaine and epinephrine after iontophoretic administration of TYMBION to the tympanic membrane.

In the OTTER study, there were no reported serious adverse events related or potentially-related to TYMBION, the IPS, the TDS or the overall procedure. In general, the non-serious adverse events were of the type and frequency consistent with expectations for tympanostomy tube placement procedures regardless of the technology utilized. The most frequently reported non-serious adverse event associated with use of the Tula® System was inadequate anesthesia. Adequacy of anesthesia was determined using a tympanic membrane tap assessment with a dull otologic instrument. There were 22 subjects who failed this assessment. Eleven subjects (4%; 11/269) failed based on inadequate anesthesia (i.e., felt discomfort during the assessment) and were counted as adverse events. Ten subjects (4%; 10/269) failed due to behavior issues or

difficult ear anatomy that precluded the tympanic membrane assessment of both ears. This suggests that while the majority of treated subjects appeared to have adequate anesthesia for successful tube placement, there were some who experienced pain, including in the moderate to severe range.

The in-office procedure was not successful in all subjects. Of the treatment failures who subsequently underwent tube placement in the operating room, all 19 (100%) of these procedures were successful. This suggests that no procedural aspects of an unsuccessful OTTER procedure impacted the ability to successfully perform a subsequent OR-based procedure at a future time.

C. Benefit-Risk Determination

The benefits of tube placement using the Tula® System have been demonstrated by the OTTER study described above. The Tula® System enables physicians to perform tympanostomy tube placement in an office setting, which previously almost universally required the administration of either monitored anesthesia care (MAC) or general anesthesia in pediatric patients. Patients and parents, clinicians, and insurers prefer, when possible, that surgical procedures be moved from the operating room to an office or other ambulatory setting. Reasons include convenience, decreased financial burden, and less exposure to sedatives or general anesthetics. The financial burden not only encompasses the overall cost of the procedure, but also includes time lost from work for either the patient or the parent. Additional benefits seen in the OTTER study include low incidence of adverse events and limited post-procedure restrictions.

The primary limitation to the widespread use of the Tula® System is the risk of inadequate anesthesia and patient intolerance. It appears that TYMBION iontophoresis is efficacious for the majority of treated subjects and mean subject-reported pain scores indicated no greater than mild pain, on average, was experienced during tube placement. There was, however, a large number of subjects in the pediatric study who reported either inadequate anesthesia or high pain scores (greater than 6 on the FPS-R) during the procedure. As previously discussed, there were 12 subjects with the adverse event of inadequate anesthesia and 22 subjects who failed the anesthesia effectiveness endpoint. In the pivotal cohort, tube tolerability was assessed in the older age group (5 to 12-year-old subjects) using the FPS-R and there were 25 subjects (out of 107 documented procedural successes) who reported pain scores of six or greater. These results suggest that the resulting tympanic membrane local anesthesia after iontophoresis is not always sufficient to perform a myringotomy and tube placement. Painful tympanostomy tube placement could traumatize patients such that subsequent office procedures, including immunizations and dental cleanings, become more challenging. Anesthetic failures of TYMBION would require tube placement in the OR under general anesthesia. It is possible that based on a variety of factors, including convenience, parents may sacrifice the certainty of adequate analgesia to avoid exposure to a general anesthetic for their child.

Patient selection appears to be a key for successful tube placement with the Tula® system. The patient must have the behavioral temperament to remain relatively still during the iontophoresis procedure, which may last up to 17.5 minutes with activation of the Reduce feature. Additionally, there may be pressure sensations during iontophoresis that may be intolerable for some patients, and the TDS emits a sound upon actuation, which may be intolerable for some patients.

The following table summarizes the benefits and risks of the Tula® system, with emphasis on TYMBION iontophoresis.

Table 22: Benefit-Risk Assessment for the Tula® System

Benefit	Risk
Procedural benefits • Local anesthesia confined to tympanic membrane • Convenient for adult and pediatric patients • No pre- or post-procedure restrictions - no *nil per os* restrictions - return to school, work, etc., same day • No additional medication administration • Low incidence of adverse events • Patient, parent preference	Procedural risks • Lower procedural success than standard of care OR-based procedure • Painful tube placement - traumatic experience - parental preference to proceed without adequate anesthesia • Prolonged iontophoresis - Reduce feature activation - pause for other reasons • Adverse events - vertigo, dizziness, ipsilateral tongue-numbness and taste changes, nausea, vomiting - local skin reaction to return electrode patch

Limitations of use includes the following:

- TYMBION is for use only with the Tula Iontophoresis System and cannot be used with any other iontophoresis device.
- TYMBION is not for use alone (i.e., without the Tula Iontophoresis System) and is not interchangeable with other lidocaine with epinephrine formulations.
- Single administration only: the safety of repeat iontophoretic administration of TYMBION has not been evaluated in humans, and repeat administration (to the same ear) is not recommended.
- Recent myringotomy or TM perforation: treatment failures may require standard of care OR tube placement
- Patient temperament, behavior

In conclusion, the Tula® System appears to have a favorable benefit-risk profile, as demonstrated in both the adult and pediatric studies, despite the risks and limitations of use associated with the system. The low incidence of reported adverse events supports the safety profile of TYMBION iontophoresis for sufficiently anesthetizing the tympanic membrane for myringotomy and tube placement. While hearing loss and histopathological changes to the tympanic membrane were reported in supra-clinical dosing groups in the nonclinical development program (i.e., ototoxicity animal studies), a causal relationship related to the

iontophoretic current, administration of TYMBION, or the TDS was not established. Many of the identified risks and potential mitigation strategies can be described in product labeling.

Patient Perspectives

The patient/parent perspective was considered during development of the OTTER study protocol and during review of the PMA. The primary effectiveness endpoint of Procedural Success was based on the results of a Patient Preference study, previously discussed. Parents expressed a strong preference for in-office tube placement using iontophoresis of TYMBION and the TDS as compared to the traditional OR-based tube placement under general anesthesia.

During the PMA review, the patient/parent perspective was evaluated through a satisfaction survey conducted at the 3-week follow-up visit. Parents overall expressed high satisfaction with the Tula procedure, and a strong preference for in-office tube placement using the Tula® System when considering a hypothetical future procedure for a sibling or family friend.

D. Overall Conclusions

The data provided in support of this marketing application demonstrate a reasonable assurance of safety and effectiveness for the Tula System when used in accordance with the indications for use and labeling. Effectiveness was demonstrated in both the adult and pediatric studies. Safety of the combination product system was established based on the lack of serious adverse events, in addition to a non-serious adverse event profile that was consistent with expectations for tympanostomy tube placement procedures in general. Inadequate anesthesia appears to be the most likely adverse event associated with iontophoretic administration of TYMBION, such that some patients will require tube placement using traditional techniques in the OR.

XIV. CDRH DECISION

CDRH issued an approval order on November 25, 2019. The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device and drug labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

[1] Kalia YN, Naik A, Garrison J, Guy RH. Iontophoretic drug delivery. Advan Drug Del Rev 56: 619-658, 2004.

[2] Henderson D and Hamernik RP. Impulse noise: Critical review, J Acoust Soc Am 80(2);569-84, 1986.

[3] Morgan DW, Wilson RH, Dirks DD. Loudness discomfort levels under earphone and in the free field: The effect of calibration. J Acoust Soc Am 56; 498-501, 1974. 105

[4] S. Gelfand. Hearing: An Introduction to Psychological and Physiological Acoustics, Fourth Edition, 2007, excerpt from p. 287, Figure 9.3.

[5] Rosenfeld RM, Schwartz SR, Pynnonen MA, Tunkel DE, Hussey HM, Fichera JS, Grimes AM et al. Clinical Practice Guideline: Tympanostomy Tubes in Children. Otolaryngol Head Neck Surg149(IS): S1-S35, 2013.

[6] Tsze DS, Hirschfeld G, Dayan PS, et al. Defining no pain, mild, moderate, and severe pain based on the faces pain scale-revised and color analog scale in children with acute pain. Pediatr Emerg Care 34(8);537-544, 2018.

[7] Boivin JM, Poupon-Lemarquis L, Iraqi W, Fay R, Schmitt C, Rossignol P. A multifactorial strategy of pain management is associated with less pain in scheduled vaccination of children: a study realized by family practitioners in 239 children aged 4 –12 years old. Fam Pract. 25(6); 423– 429, 2008.

[8] Berberich FR, Landman Z. Reducing immunization discomfort in 4- to 6-year-old children: a randomized clinical trial. Pediatrics. 124(2);e203-9, 2009.

[9] Asvanund Y, Mitrakul K, Juhong RO, Arunkal M. Effect of audiovisual eyeglasses during local anesthesia injections in 5- to 8-year-old children. Quintessence Int; 46(6):513-521, 2015.

[10] Kamath PS. A novel distraction technique for pain management during local anesthesia administration in pediatric patients. J Clin Pediatric Dent; 38(1):45-47, 2013.

[11] Deepak V, Challa RR, Kamatham R, and Nuvvula S. Comparison of a new auto-controlled injection system with traditional syringe for mandibular infiltrations in children: A randomized controlled trial. Anesth Essays Res 11(2); 431-438, 2017.

[12] Taddio A, Soin HK, Schuh S, Koren G, Scolnik D. Liposomal lidocaine to improve procedural success rates and reduce procedural pain among children: a randomized controlled trial. CMAJ. 172(13); 1691–1695, 2005.

[13] Karakaya A, Gozen D. The Effect of Distraction on Pain Level Felt by School-age Children During Venipuncture Procedure--Randomized Controlled Trial. Pain Manag Nurs 17(1); 47-53, 2016.

[14] Inal S, Kelleci M. Relief of pain during blood specimen collection in pediatric patients. MCN Am J Matern Child Nurs 37(5); 339-345, 2012.

[15] Hicks CL, von Baeyer CL, Spafford PA, et al. The Faces pain scale-revised: toward a common metric in pediatric pain measurement. Pain, 2001; 93: 173-183.