



# **XprESS Eustachian Tube Dilation Study**

**Investigational Plan Number 2909-001**

**REVISION C**

**September 2015**

**Entellus Medical Inc.**

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This study will be conducted in accordance with the protocol and applicable regulatory requirements.

## **CONFIDENTIAL INFORMATION**

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## Investigational Plan Summary

<b>Title:</b>	XprESS Eustachian Tube Dilation Study
<b>Study device:</b>	XprESS™ Multi-Sinus Dilation System (XprESS device)
<b>Study design:</b>	A prospective, multicenter, 2-phase, controlled study. Phase 1 consists of a nonrandomized design. Phase 2 consists of a randomized design.
<b>Enrollment:</b>	A total of 50 subjects: Phase 1 – 10 nonrandomized balloon dilation subjects Phase 2 – 40 subjects randomized 1:1 to balloon dilation (treatment) or continued current medical therapy (control)
<b>Treatment:</b>	Phase 1: All subjects will receive balloon dilation Phase 2: Subjects will be randomized 1:1 to the following study arms: <ol style="list-style-type: none"><li>1. Control arm: Continued current medical management with ability to crossover to dilation after 6 weeks, if not improved</li><li>2. Treatment arm: Eustachian tube dilation – bilateral or unilateral, as indicated</li></ol>
<b>Clinical centers:</b>	Up to 7 US investigational centers
<b>Inclusion criteria:</b>	Subjects <u>MUST</u> : <ol style="list-style-type: none"><li>1. Be <math>\geq 18</math> years old</li><li>2. Have been diagnosed with Eustachian tube dysfunction (ETD) for no less than 12 months before enrollment with 3 or more of the following symptoms: ear pain, ear pressure, ringing in the ears, cracking or popping sounds in the ears, muffled hearing, or feeling that ears are clogged or “under water”</li><li>3. Have an overall ETDQ-7 score <math>\geq 3.0</math></li><li>4. Have a record of failed medical management for ETD consisting of a minimum of either 4 weeks of daily intranasal steroid spray or 1 completed course of an oral steroid within the 12-month period before enrollment</li><li>5. Be a candidate for unilateral or bilateral transnasal balloon Eustachian tube dilation using the XprESS device</li><li>6. Have a temporal bone CT scan (showing the Eustachian tube) without contrast within 6 months of the enrollment date</li><li>7. Be able to read and understand English</li><li>8. Be able and willing to provide consent</li><li>9. Be willing to comply with the protocol requirements</li></ol>
<b>Exclusion criteria:</b>	Subjects <u>MUST NOT</u> : <ol style="list-style-type: none"><li>1. Have had any head or neck surgery (eg, adenoidectomy, tonsillectomy) including sinonasal surgery or ear tube placement performed within 3 months before enrollment</li><li>2. Require concomitant procedures at the time of study enrollment or procedure</li><li>3. Have ear tubes in place (tympanostomy tubes, myringotomy tubes, ventilation tubes, or pressure equalization tubes) or perforation of the tympanic membrane at the time of the study enrollment or procedure (patients with healed tympanic membranes after extrusion of tubes are not excluded)</li></ol>

4. Have patulous Eustachian tubes
5. Have had any previous laser tuboplasty surgery or microdebridement
6. Have temporomandibular joint (TMJ) disorders
7. Have early hydrops (Meniere's disease)
8. Have had head or neck radiation therapy or sinonasal malignancy
9. Have a diagnosis of chronic rhinosinusitis (CRS/RARS) that is uncontrolled
10. Have an immunodeficiency
11. Have craniofacial abnormalities or other anatomical conditions (eg, severely deviated septum, tumor, enlarged adenoids or tonsils, severe turbinate hypertrophy) that would prevent transnasal access of the Eustachian tubes
12. Have evidence of internal carotid artery dehiscence or anatomic abnormalities
13. Have uncontrolled allergies
14. Have unmanaged gastroesophageal reflux disease (GERD) or laryngopharyngeal reflux (LPR)
15. Be pregnant at the time of study enrollment or procedure
16. Be currently participating in any other drug or device clinical studies excluding postapproval or marketing registry studies

<b>Objective:</b>	To demonstrate the safety and efficacy of the XprESS device in treating patients with ETD.
<b>Primary endpoints:</b>	<ul style="list-style-type: none"> <li>• Comparison of mean change in overall ETDQ-7 scores from baseline to 6 weeks between randomization arms</li> <li>• Complication rate</li> </ul>
<b>Secondary endpoints:</b>	<ul style="list-style-type: none"> <li>• Mean change in overall ETDQ-7 score from baseline to follow-up (balloon dilation subjects)</li> <li>• Technical success rate</li> <li>• Revision dilation rate</li> </ul>
<b>Study assessments</b>	<ul style="list-style-type: none"> <li>• Baseline</li> <li>• 6-Week crossover evaluation (control subjects only)</li> <li>• Procedure</li> <li>• 6-Week postprocedure follow-up</li> <li>• 3-Month postprocedure follow-up</li> <li>• 6-Month postprocedure follow-up (for 510(k) submission and publication purposes)</li> <li>• 12-Month postprocedure follow-up (for publication purposes)</li> </ul>
<b>Sponsor:</b>	Entellus Medical Inc. United States
<b>Data management and monitoring:</b>	Entellus Medical Inc. United States

## Abbreviations and Acronyms

AE	Adverse event
ANSI	American National Standards Institute
CFR	Code of Federal Regulations (US)
CI	Confidence interval
CRF	Case report form
CRS/RARS	Chronic rhinosinusitis/recurrent acute rhinosinusitis
CT	Computed tomography
DICOM	Digital Imaging and Communications in Medicine
ENT	Ear, nose, and throat
EQ-5D	EuroQol-5 dimension survey
ET	Eustachian tube
ETD	Eustachian tube dysfunction
ETDQ-7	Eustachian tube dysfunction 7-item questionnaire
FDA	Food and Drug Administration (US)
GCP	Good clinical practices
GERD	Gastroesophageal reflux disease
HIPAA	Health Insurance Portability and Accountability Act of 1996 (US)
ICF	Informed consent form
IFU	Instructions for use
IRB	Institutional Review Board
LPR	Laryngopharyngeal reflux
PTA	Pure tone audiometry
SAE	Serious adverse event
UADE	Unanticipated adverse device effect
VAS	Visual analog scale

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# 1 Background and Purpose

## 1.1 Background

The Eustachian tube (ET) connects the middle ear to the nasopharynx. It serves 3 functions: pressure regulation, deflection of pathogens/foreign objects, and middle ear fluid clearance.<sup>1</sup> The ET is comprised of a bony isthmus and a cartilaginous region. The cartilaginous part of the ET is normally closed but opens when needed to equalize pressure within the middle ear. Transient opening of the ET occurs with yawning, swallowing, or popping of the ears.

Dysfunction of the Eustachian tube can result from the tube being too open (patulous ET), too closed (mechanical obstruction), or unable to efficiently open during swallowing (functional obstruction).<sup>2</sup> Mechanical obstruction of the ET can be from either extrinsic (eg, tumors, adenoids, nasal septal deviations) or intrinsic (eg, inflammation, stenosis) mechanisms. Functional obstruction, a common cause of Eustachian tube dysfunction (ETD), occurs when the tube fails to open in the absence of a mechanical obstruction and can be caused by increased tubal compliance, inefficient opening mechanism, and/or abnormal pressures at either ET end.<sup>2</sup>

When the ET does not function properly there is abnormal pressure equalization in the middle ear. Symptoms of ETD include fullness in the ear, dizziness, tinnitus, and pain or discomfort with barometric changes (eg, flying, diving). ETD can lead to tympanic membrane retraction, cholesteatoma, and hearing loss and is frequently associated with chronic otitis media. Chronic rhinosinusitis, allergic rhinitis, gastroesophageal reflux disease, and smoking exposure may all have roles in development of ETD.

Historically, treatments have been geared toward management or prevention of otitis media, not correcting the dysfunction of the ET. Recently, research has been initiated to study the possibility that balloon dilation could offer a minimally invasive treatment for ETD. It is thought that ET balloon dilation increases the luminal diameter, reduces local inflammation, and facilitates the muscular action necessary for ET opening.<sup>3</sup> Theoretically, balloon dilation results in minimal mucosal injury, sparing the clearance and protective functions of the ET, while improving pressure equalization within the middle ear.

## 1.2 Purpose

The purpose of the current study is to collect 6-month safety and efficacy data on the use of the XprESS device to support a 510(k) application to FDA to add a new indication for use. Six- and 12-month data will also be collected for publication purposes.

## 2 Protocol

### 2.1 Study design

The study is a prospective, multicenter, 2-phase, controlled study. Phase 1 will include 10 subjects treated with balloon dilation.

Phase 2 will include 40 subjects randomized 1:1 to balloon dilation or control (6 weeks of continued current medical therapy). Phase 2 is designed to test the primary efficacy endpoint hypothesis that ETD symptom improvement (overall ETDQ-7 score) after balloon dilation is superior to the control group. For subjects randomized to the control arm, if ETD symptoms persist at 6 weeks after randomization (overall ETDQ-7 score  $\geq 3.0$  or change  $< 0.4$ ), the subjects will be allowed to crossover to the balloon dilation arm. Control subjects who do not have persistent ETD symptoms at 6 weeks after randomization will be exited from the study. **Figure 1** presents the study design and subject flow for Phase 2.

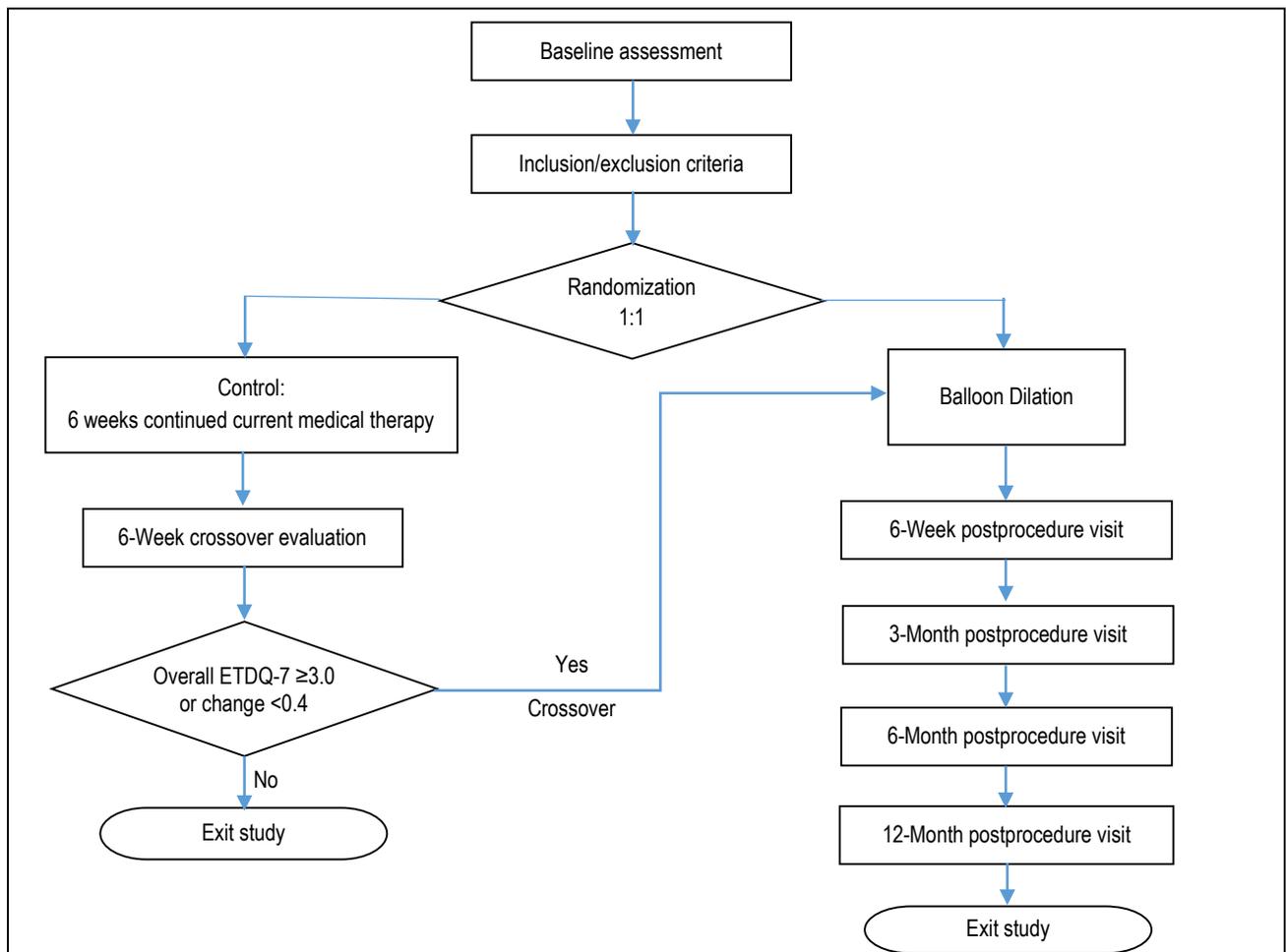


Figure 1. Phase 2 Study Design and Subject Flow

## 2.2 Study objective

The primary objective of the study is to demonstrate the safety and efficacy of the XprESS device for treating patients with Eustachian tube dysfunction (ETD).

## 2.3 Study endpoints

### 2.3.1 Primary endpoints

The following measures will be collected as the primary endpoints:

- Comparison of mean change in overall ETDQ-7 score from baseline to 6 weeks between balloon dilation arm and control arm
- Complication rate

### 2.3.2 Secondary endpoints

The following measures will be collected as secondary endpoints:

- Mean change in overall ETDQ-7 score from baseline to follow-up (balloon dilation subjects)
- Technical success rate
- Revision dilation rate

## 2.4 Study size and duration

Initially, up to 10 subjects will be enrolled at up to 3 US investigational centers and treated with balloon dilation (phase 1). The second phase will include enrollment of an additional 40 subjects randomized 1:1 to balloon dilation or continued current medical therapy (control) at up to 7 investigational centers. Additional subjects may be added as needed upon approval from FDA.

It is anticipated that the first 10 subjects from phase 1 will be pooled with the remaining balloon dilation subjects for the final analysis cohort based on similar inclusion/exclusion criteria and data collection.

The expected duration of the study is 17 to 24 months. It is estimated that enrollment will take from 6 to 12 months. When a minimum of 34 phase 2 subjects have completed 6 weeks of follow-up, and a minimum of 25 phase 1 and phase 2 subjects treated with balloon dilation have completed at least 6 months of follow-up, a 510(k) application will be submitted to the FDA to obtain clearance for the new indication. All treated subjects will continue follow-up through 12 months for publication purposes. Control subjects who do not crossover to the balloon dilation treatment will be exited from the study at 6 weeks after randomization.

## 2.5 Study hypothesis

The study is designed to test the primary efficacy endpoint hypothesis that ETD symptom improvement after balloon dilation is superior to the control group.

The following hypothesis will be tested in the comparison of mean change from baseline in overall ETDQ-7 scores at 6 weeks using a 1-sided Student's t-test where a p value less than 0.025 will be considered statistically significant:

Ho:  $d \geq 0$

Ha:  $d < 0$

Where  $d$  is the difference between balloon dilation and control group (balloon dilation – control) for the mean change from baseline to 6 weeks in the overall ETDQ-7 score.

## 2.6 Sample size estimation

The sample size was calculated using PASS, Inequality Tests for Two Means (2-sample t-test) to test for superiority of improvement of ETDQ-7 scores at 6 weeks and was based on the following assumptions:

- Significance level (1-sided alpha) = 0.025
- Power = 80%
- Mean change in overall ETDQ-7 score in the balloon dilation group = -2.15
- Mean change in overall ETDQ-7 score in control group = -0.85
- Common standard deviation for both groups = 1.3

Under the assumptions outlined above, a total sample size of 34 randomized subjects (17 per arm) is adequate to test this hypothesis. To account for up to 10% attrition, a minimum of 40 subjects will be enrolled in Phase 2 of the study.

## 2.7 Data analyses

Summary statistics will be calculated for all study endpoints. Categorical variables will be summarized using frequency distributions and continuous variables will be summarized with means, standard deviations, and ranges. Confidence intervals (95% CI) may be computed for select study endpoint measures. The primary efficacy endpoint will be tested at a 1-sided alpha level of 0.025. The secondary endpoint of the mean change in the overall ETDQ-7 score from baseline to follow-up in subjects treated with balloon dilation will be tested at a 2-sided alpha level of 0.05.

Subjects who are randomized but drop out before receiving their randomized treatment (balloon dilation or completion of the 6-week continued medical therapy) will not be included in the data analysis.

### 2.7.1 Poolability analysis

Poolability of the primary efficacy endpoint between investigational centers will be evaluated. This assessment will evaluate the significance of any differences or imbalances that exist across investigational centers in the primary endpoint. Centers with less than 5 patients enrolled will be combined into a pseudocenter for purposes of analysis. To protect against having an overly large pseudocenter, when one pseudocenter exceeds 5 subjects, a second pseudocenter will be formed. This process will continue as needed each time a pseudocenter exceeds 5 subjects.

The type III p value from an ANOVA model will be used to assess center poolability for the primary efficacy endpoint. An alpha level of 0.15 will be used to assess statistical significance of the center effect.

### 2.7.2 Missing data

Missing data can impact the integrity and credibility of any clinical study. Therefore, all attempts will be made to minimize missing data. These attempts include training of the investigators and site personnel and discussions with the subjects during the informed consent process on the importance of accurate and complete data collection. The study sponsor will track issues with sites regarding missing data through the usual monitoring process. Analyses that account for missing data will be conducted on the primary efficacy endpoint for a change from baseline.

## 2.8 Study population

The study population is patients 18 years and older with medically refractory ETD. To be eligible for enrollment in the study the patients must meet all the inclusion criteria and none of the exclusion criteria.

### 2.8.1 Inclusion criteria

Subjects MUST:

1. Be  $\geq 18$  years old
2. Have been diagnosed with ETD for no less than 12 months before enrollment with 3 or more of the following symptoms: ear pain, ear pressure, ringing in the ears, cracking or popping sounds in the ears, muffled hearing, or feeling that ears are clogged or “under water”
3. Have an overall ETDQ-7 score  $\geq 3.0$
4. Have a record of failed medical management for ETD consisting of a minimum of either 4 weeks of daily intranasal steroid spray or 1 completed course of an oral steroid within the 12-month period before enrollment
5. Be a candidate for unilateral or bilateral trans-nasal balloon Eustachian tube dilation using the XprESS device
6. Have a temporal bone CT scan (showing the Eustachian tube) without contrast within 6 months of the enrollment date
7. Be able to read and understand English
8. Be able and willing to provide consent
9. Be willing to comply with the protocol requirements

### 2.8.2 Exclusion criteria

Subjects MUST NOT:

1. Have had any head or neck surgery (eg, adenoidectomy, tonsillectomy) including sinonasal surgery or ear tube placement performed within 3 months before enrollment
2. Require concomitant procedures at the time of study enrollment or procedure
3. Have ear tubes in place (tympanostomy tubes, myringotomy tubes, ventilation tubes, or pressure equalization tubes) or perforation of the tympanic membrane at the time of the study enrollment or procedure (patients with healed tympanic membranes after extrusion of tubes are not excluded)
4. Have patulous Eustachian tubes

5. Have had any previous laser tuboplasty surgery or microdebridement
6. Have temporomandibular joint (TMJ) disorders
7. Have early hydrops (Meniere's disease)
8. Have had head or neck radiation therapy or sinonasal malignancy
9. Have a diagnosis of chronic rhinosinusitis (CRS/RARS) that is uncontrolled
10. Have an immunodeficiency
11. Have craniofacial abnormalities or other anatomical conditions (eg, severely deviated septum, tumors, enlarged adenoids or tonsils, severe turbinate hypertrophy) that would prevent transnasal access of Eustachian tubes
12. Have evidence of internal carotid artery dehiscence or anatomic abnormalities
13. Have uncontrolled allergies
14. Have unmanaged gastroesophageal reflux disease (GERD) or laryngopharyngeal reflux (LPR)
15. Be pregnant at the time of study enrollment or procedure
16. Be currently participating in any other drug or device clinical studies excluding postapproval or marketing registry studies

## 2.9 Methods and procedures

Study methods and procedures are described below. An overview of the required Phase 2 study assessments at each follow-up visit is provided in **Table 1**. Each subject's follow-up schedule is based on the date of randomization (control arm) or the study procedure (balloon dilation arm and crossover subjects).

Table 1. Phase 2 Study Assessment Schedule

Study evaluation	Baseline Within 60 days of procedure for balloon dilation arm	6-Week crossover evaluation (control arm only) ± 7 days	Procedure Within 60 days of baseline or 6-week crossover evaluation	6-Week post procedure ± 7 days	3-Month post procedure ± 15 days	6-Month post procedure ± 30 days (for 510(k) and publication)	12-Month post procedure ± 45 days (for publication)
Informed consent	✓						
Eligibility assessment	✓	✓					
Demographics/history	✓						
CT scan without contrast	✓ <sup>a</sup>						
Symptoms/exam	✓	✓		✓	✓	✓	✓
Medications <sup>b</sup>	✓	✓	✓	✓	✓	✓	✓
Nasal endoscopy	✓	✓		✓	✓	✓	✓
Otoscopy examination	✓	✓		✓	✓	✓	✓
Tympanometry	✓	✓		✓	✓	✓	✓
Valsalva evaluation	✓	✓		✓	✓	✓	✓
EQ-5D questionnaire	✓	✓		✓	✓	✓	✓
ETDQ-7 questionnaire	✓	✓		✓	✓	✓	✓
Ear infection assessment	✓ <sup>c</sup>			✓	✓	✓	✓

Study evaluation	Baseline Within 60 days of procedure for balloon dilation arm	6-Week crossover evaluation (control arm only) ± 7 days	Procedure Within 60 days of baseline or 6-week crossover evaluation	6-Week post procedure ± 7 days	3-Month post procedure ± 15 days	6-Month post procedure ± 30 days (for 510(k) and publication)	12-Month post procedure ± 45 days (for publication)
Audiologic examination	✓					✓	
Pregnancy test (when applicable)	✓		✓				
Procedure pain			✓ <sup>d</sup>				
Technical success			✓				
Device malfunction			✓				
Adverse events		✓	✓	✓	✓	✓	✓
Revision dilation or additional surgery				✓	✓	✓	✓
Subject satisfaction				✓	✓	✓	✓

<sup>a</sup> The eligibility CT scan can be performed within 6 months of enrollment.  
<sup>b</sup> Only ENT-related medications will be recorded (eg, antibiotics, steroids, allergy treatment, decongestants).  
<sup>c</sup> At baseline, determine the number of ear infections in the 12-month period before enrollment.  
<sup>d</sup> The pain scale should be completed before discharge from the index procedure. Subjects treated under general anesthesia are not required to assess procedure pain.

### 2.9.1 Eligibility assessment

Patients are considered eligible for this study if they meet **all** the inclusion criteria and **none** of the exclusion criteria as defined in **Section 2.8**. The principal investigator or subinvestigator at each investigational center will determine patient eligibility based on the inclusion/exclusion criteria.

All potential subjects must have a CT scan (without contrast) of the temporal bone done within 6 months before study enrollment. The CT scan must include coronal and axial images of the temporal bone including the Eustachian tube. Two electronic copies in DICOM format of the CT scan must be available; 1 copy to be retained by the investigational center and 1 copy to be retrieved by the sponsor.

### 2.9.2 Baseline visit

All candidates for the study will have the following baseline clinical evaluations done **before enrollment and randomization**:

- Informed consent signed
- Baseline medical history, demographics, symptoms, and medication history in the 12-month period before enrollment
- Eligibility assessment: subjects meet all inclusion and no exclusion criteria.
- Nasal endoscopy
- Otoscopy examination
- Tympanometry
- Valsalva evaluation

- Assessment of ear infections over the 12-month period before enrollment
- Audiologic examination including a pure tone auditory (PTA) test
- EQ-5D and ETDQ-7 QOL questionnaires (completed by the study subject)
- Pregnancy test for female subjects of childbearing potential

The results of all baseline evaluations will be documented on the appropriate Case Report Forms (CRFs).

For subjects undergoing balloon dilation, preprocedure antibiotics and steroids may be prescribed at the discretion of the study physician. Medications may be prescribed to treat active infections and procedures may be rescheduled until active infections resolve.

### 2.9.3 Enrollment

A patient will be considered enrolled in the study after the baseline assessment once all the inclusion/exclusion criteria have been met and at the time of randomization.

### 2.9.4 Randomization

Randomization assignments will be generated by an independent statistician using a distribution in variable blocks sizes for each center with a 1:1 allocation to control or balloon dilation. The master randomization list will be stored by the Sponsor. Randomization assignments will be placed into sequentially numbered and sealed envelopes. The trained study center personnel will contact Sponsor to receive the randomization assignment after the following steps have been completed:

1. All baseline evaluations have been performed
2. Subject has been determined eligible for the study (ie, inclusion/exclusion criteria reviewed)
3. Subject has signed an Informed Consent

The Sponsor will retrieve the first (or next) sequentially numbered envelope for that center and open it. The randomization assignment, including the randomization ID number and treatment assignment, will be recorded on the Randomization Enrollment Case Report Form. The Sponsor personnel will record the subject ID in the randomization log.

### 2.9.5 Control arm assignment

Subjects randomized to the control arm will continue their current ETD medical treatment regimen for 6 weeks after randomization. A treatment regimen consisting of no medication is permitted if consistent with the subject's current treatment plan. Medications will be documented on the Medications CRF. Control subjects are not allowed to undergo any surgical treatments during this study period.

After the 6-week period of continued medical therapy, control subjects who continue to have ETD symptoms (defined as an overall ETDQ-7 score  $\geq 3.0$  or a change of  $< 0.4$ ) will be allowed to crossover to balloon dilation treatment and will undergo the dilation procedure and postprocedure follow-up visit schedule for the balloon dilation arm. Control subjects who do not

crossover will be exited from the study at this time. The 6-week crossover evaluation will serve as the preprocedure assessment for crossover subjects.

#### 2.9.6 Balloon dilation arm assignment and procedure

Subjects should undergo the balloon dilation procedure within 60 days of the baseline assessment (randomized to balloon dilation) or the 6-week crossover evaluation (crossover subjects). All female subjects of childbearing potential are required to have a negative blood or urine pregnancy test **within 10 days before a balloon dilation procedure**.

Refer to the XprESS Instructions for Use (IFU) for specific instructions on system preparation, subject preparation, device set-up, shaping the device, and detailed treatment procedure for using XprESS to perform Eustachian tube dilation.

#### *Procedure site of service*

Investigators may choose to complete study procedures under general plus local anesthesia in a surgical setting or under local anesthesia alone in the office setting based on their medical discretion and subject tolerance. If the study procedure is first attempted in the office setting but cannot be completed under local anesthesia alone due to subject tolerance, the subject may be treated under general anesthesia in a surgical setting without being withdrawn from the study. Such cases will not be considered treatment failures. Procedures converted from local anesthesia alone to general anesthesia will be documented on the Procedure CRF.

#### *Procedure anesthesia*

Anesthesia should be administered appropriately to allow subject tolerance and based on the treating physician's medical training. Physicians may choose to use general and/or local anesthesia regimens that will allow safe and tolerable use of the device in the subject. Type of anesthesia and location of local injections will be documented.

#### *Eustachian tube assessment*

A temporal CT scan with axial and coronal views performed within the last 6 months before study enrollment will be reviewed to ensure there are no anatomic anomalies that would prevent transnasal access to the Eustachian tube or put the subject at increased risk (eg, dehiscence of the carotid artery). If such conditions exist, the subject is not eligible for the study.

#### *Device size selection*

Investigators may choose the XprESS device size based on their medical knowledge and the subject's Eustachian tube anatomy. All balloon sizes are appropriate for treating Eustachian tubes; selection is based on physician preference. The XprESS device sizes are listed in **Section 4.1**.

#### *Eustachian tube balloon dilation*

The XprESS balloon is designed for a transnasal approach only. Procedural information on device use is provided in the XprESS IFU.

The following data will be collected during the study procedure and documented on the appropriate CRFs:

- Site of service
- Admission and discharge date/times
- Procedure start/stop times
- Type of anesthesia and location and dosage of any local injections
- Identification of all XprESS devices used
- Technical success for XprESS device
- Total number of balloon inflations for each treatment side
- Total duration of balloon inflations (in seconds) for each treatment site
- Procedures that convert from local anesthesia alone to general anesthesia
- Procedure pain score (for subjects treated under local anesthesia alone; not required for subjects who are treated under general anesthesia)
- Adverse events
- Device malfunctions

#### *Postprocedure care*

Postprocedure care, including medical management, is at the discretion of the physician. Postprocedure medical and clinical management will be collected on the Medication CRF at the 6-week postprocedure visit.

#### *Concomitant procedures*

Concomitant procedures are not allowed in this study. Specifically, subjects randomized to the control arm are not allowed to undergo any surgical procedures of the ears or sinuses during the 6-week period of continued medical therapy.

#### 2.9.7 Follow-up visits

Subjects randomized to the control arm are scheduled for a follow-up visit at 6 weeks ( $\pm 7$  days) after their randomization. At this visit, control subjects will be evaluated and if their ETD symptoms persist (defined as overall ETDQ-7 score  $\geq 3$  or change  $< 0.4$ ), the subjects are eligible for crossover to balloon dilation treatment. Subjects who do not have persistent ETD symptoms are exited from the study after completion of this visit.

Subjects randomized to balloon dilation and crossover subjects are scheduled for the following postprocedure follow-up visits (window):

- 6-Week ( $\pm 7$  days)
- 3-Month ( $\pm 15$  days)
- 6-Month ( $\pm 30$  days)
- 12-Month ( $\pm 45$  days)

The following assessments are required at all follow-up visits:

- Symptom assessment
- Nasal endoscopy examination
- Otoscopy examination

- Tympanogram
- Valsalva evaluation
- Medication use since last study visit
- Ear infections since last study visit
- Revision dilation or additional surgery
- Subject satisfaction
- EQ-5D
- ETDQ-7
- Adverse events

In addition to the assessments noted above, an **audiologic examination is required at the 6-month visit.**

#### 2.9.8 Revision dilations or additional surgery

Revision dilations or other surgical procedures are permitted for subjects who do not experience relief of ETD symptoms after balloon dilation treatment. However, it is recommended that revision procedures are not performed before the majority of tissue healing/remodeling has been allowed to occur. This process can take up to 3 months after the initial procedure. Standard of care medical treatment is permitted at any time during the study to address subject symptoms.

If a subject has a revision dilation or additional ENT surgery during the postprocedure follow-up period, the investigational center should make every effort to collect the procedure/operative notes for the procedure(s). The date and type of procedure performed will be documented on the Revision Dilation/Additional Surgery CRF. A copy of the deidentified revision procedure notes will be retrieved for the sponsor study files.

#### 2.9.9 Early withdrawal and lost to follow-up

Study subjects are free to withdraw from the investigation at any time without having to justify their reasons and without affecting their relationship with the investigator. An investigator may also withdraw a subject from the study at any time if it is determined to be in the subject's best interests.

A subject's future management will not be changed by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain subjects until completion of the clinical study. Reasons for termination or withdrawal include but are not limited to the following:

- Subject death
- Subject request
- Subject lost to follow-up. A subject is considered "lost to follow-up" after a minimum of 2 documented attempts to reach the subject by phone call by a member of the study staff and an unanswered certified letter sent to the subject's last known address by a traceable method (eg, certified mail, courier, commercial shipping/transport company)
- Subject's participation terminated by the investigator

- Study terminated by the sponsor

For any subjects with early withdrawal or termination, termination information will be recorded in the subject's records and the date of last contact with the subject noted on the End of Study CRF.

#### 2.9.10 End of study

Subjects randomized to the control arm who do not crossover to balloon dilation treatment are exited upon completion of the 6-week crossover evaluation.

Participation in the study is considered complete for all balloon dilation and crossover subjects upon completion of the 12-month postprocedure visit.

If a subject has an XprESS device inserted transnasally but does not undergo a balloon dilation procedure, the subject will be followed to the 6-week postprocedure visit and then discontinued from the study unless the subject has an ongoing adverse event (AE). If the subject has an ongoing AE at the 6-week postprocedure visit, the subject will be followed until AE resolution or 12 months post procedure, whichever comes first.

An End of Study CRF will be completed when the subject has completed their last required follow-up visit or at the time of withdrawal or lost to follow-up if the subject discontinues the study prematurely.

### 2.10 Study assessments and data collection

Study data will be collected according to Good Clinical Practices using paper CRFs completed at the investigational center. CRFs will be collected from the centers and will be entered into a ClinDex database by Entellus staff using 2-pass entry procedures. The data will be reviewed by Entellus staff and any queries will be documented and submitted to the investigational center for clarification.

The required study assessments for each specified interval are outlined in the **Section 2.9**. See **Table 1** for an overview of the required study assessments at each follow-up visit. Each subject's follow-up schedule is based on the date of randomization (control arm) or the study procedure (balloon dilation and crossover arms).

#### 2.10.1 Primary and secondary endpoint assessments

##### *Mean change in overall ETDQ-7 score*

The Eustachian Tube Dysfunction Questionnaire (ETDQ-7) is a standardized, 7-item questionnaire designed to assess quality of life associated with Eustachian tube dysfunction. The 7 dimensions of the questionnaire are pressure, pain, feeling clogged, cold/sinusitis problems, crackling/popping, ringing, and feeling muffled. Each item is assessed on a 1 (no problem) to 7 (severe problem) scale and an overall score, which is the mean of the 7 dimension scores, is calculated. The questionnaire is designed to be self-completed by the subject. ETDQ-7 questionnaires will be completed at baseline and at all study visits. Changes in overall ETDQ-7 scores will be based on the mean change between the baseline assessment (or 6-week crossover

evaluation for crossover subjects) and each follow-up assessment. Standard treatment effect size may also be calculated for the mean overall ETDQ-7 score. The ETDQ-7 CRF may be considered a source document if completed directly by the subject on the CRF.

#### *Complication rate*

A complication is defined as a serious adverse event that is device-related or procedure-related as noted in **Section 6**. The parameter of interest is the percent of subjects who experience 1 or more complications from the time of the index procedure through the 6-month follow-up.

#### *Technical success*

Technical success will be collected for each Eustachian tube in which dilation is attempted. Success of the XprESS device will be calculated as the number of successful dilations divided by the number of ETs with dilation attempts. Success is defined as an attempt where the XprESS device is successfully delivered to the target location, inflated, deflated, and withdrawn from the treated Eustachian tube.

#### *Revision dilation rate*

Revision dilation is defined as any repeat balloon dilation procedure performed on an ET that was initially treated with an XprESS device. The parameter of interest is the percent of subjects who experience 1 or more revision dilations during the study.

### 2.10.2 Other measure assessments

#### *General quality of life assessment*

Quality of life regarding general health will be assessed using the EuroQol (EQ-5D).

The EQ-5D is a standardized questionnaire used to evaluate general health-related quality of life. The questionnaire is made up of 5 questions (1 for each health dimension measured: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a visual analog scale (VAS) to indicate overall health on a scale of 0 to 100. Each health dimension has 5 possible responses: no problems, slight problems, moderate problems, severe problems, or extreme problems. The questionnaire is designed to be self-completed by the subject. The EQ-5D questionnaire will be completed at all study visits. The EQ-5D CRF may be considered a source document if completed directly by the subject on the CRF.

#### *Procedure pain*

The procedure pain assessment will be collected before discharge from each subject who undergoes the dilation procedure with local anesthesia alone. Pain will be assessed using an 11-point VAS. The Procedure CRF may be considered the source document for the procedure pain assessment.

#### *Otoscopy findings*

Otoscopy examinations will be performed at baseline and at each follow-up visit. The examination will include assessment of the tympanic membrane (ear drum) for color, translucency, mobility, shape (bulging, retraction), and the appearance of bubbles. The ear canal

will be observed for edema, fluid/pus, or cerumen (wax). For evaluation, otoscopy findings will be categorized as normal (within normal limits) or abnormal (1 or more characteristic not within normal limits). Results of the otoscopic examination will be documented on the Baseline or Follow-up CRF, as appropriate.

#### *Tympanometry*

Tympanometry will be performed at baseline and at each follow-up visit. The test will be performed with a 226 Hz signal and a copy the tympanogram will be filed with the subject study files. The following parameters from the tympanogram will be documented on the Baseline or Follow-up CRF, as appropriate:

- Peak pressure (daPa)
- Compliance (cm<sup>3</sup>)
- Ear canal volume (mL)
- Type (A, B, or C)

#### *Valsalva maneuver*

Each subject will attempt to perform a Valsalva maneuver at baseline and at each follow-up visit after tympanometry is completed. The maneuver is performed by forcing expiration with closed mouth and nostrils which increases the pressure in the middle ear. This typically results in opening of the Eustachian tube with relief of ear congestion. Popping and/or clicking are often heard during the maneuver. If the subject does not experience clearing, popping, or clicking in the ears after attempting the maneuver, the result is considered negative. Results of the Valsalva maneuver will be documented as appropriate.

#### *Ear infection frequency and healthcare visits*

The number of ear infections experienced in the 12-month period before enrollment will be recorded at the baseline visit. At each follow-up visit, the number of ear infections since the last visit will be recorded.

Similarly, the number of physician/nurse visits for ETD-related issues will be recorded and compared between the 12 months before and 12 months after balloon dilation.

#### *Subject satisfaction*

At each follow-up visit, balloon dilation and crossover subjects will be asked to indicate their satisfaction with the procedure outcome and whether they would recommend the procedure to their friends/family. The subject satisfaction questions will be documented on the ETDQ-7 CRF, which may be considered the source document for the satisfaction ratings.

#### *Audiologic examination*

An audiologic examination will be performed on all subjects at baseline and on all balloon dilation and crossover subjects at the 6-month follow-up.

Audiometry procedures should be conducted in compliance with the ANSI Method for Manual Pure-Tone Threshold Audiometry, ANSI S3.21-1978 (R1997). Computerized or self-recording audiometers should be used according to their manufacturer's instructions.

Pure tone (air-bone gap) audiometry testing will be performed using pulsed tones with the better ear, if known, tested first. The preferred frequency sequences for air and bone conduction measures are shown in **Table 2**. If masking is used, the type and level should be noted on the CRF. The air-bone gap will be calculated and reported on the CRF.

Table 2. Preferred Frequency (Hz) Testing Sequence for Air-bone Conduction Tests

Test Order	1	2	3	4	5	6	7
Air	1000	2000	4000	8000	1000 <sup>a</sup>	500	250
Bone	1000	2000	4000	1000 <sup>a</sup>	500		

<sup>a</sup> When testing the second ear, the repeat 1000 Hz test is not necessary before testing the lower frequencies.

## 3 Risk/Benefit Analysis

### 3.1 Benefits

Participation in this study is voluntary; however, information gathered from this study will be used to apply for FDA clearance of a new indication for the XprESS device for Eustachian tube dilation. Subjects with ETD may experience an improvement in their symptoms.

### 3.2 Potential risks

Study subjects will be informed of all known potential side effects and complications associated with study treatment and study assessments before consenting for the study. The risks associated with participating in the study are the same as those that the subject would have if treated with transnasal Eustachian tube balloon dilation outside of the study. These potential risks include:

- Complications from anesthesia
- Pain
- Bruising and swelling
- Bleeding
- Infection
- Continued or worsening symptoms
- Revision surgery
- Tinnitus
- Preauricular emphysema
- Damage to the ET
- Patulous ET
- Permanent hearing loss
- Tympanic membrane damage
- Carotid artery damage
- Cerebrospinal fluid leak

### 3.3 Risk mitigation

The protocol has been developed to minimize the risks for the subject in a number of ways. Sample size was calculated to expose the smallest number of subjects while still being able to adequately test the study objectives. The subject selection criteria were designed to minimize risk by excluding patients who have comorbidities or conditions that may put the patient at higher risk for the balloon dilation procedure. Concomitant procedures that could increase risk and confound study results are not permitted during the study. The subjects are closely monitored by frequent follow-up visits during the study. Finally, the selected investigators are experienced in endoscopic surgery, specifically trained on use of the XprESS device, and expected to comply with the manufacturer's IFU for the XprESS device for Eustachian tube dilation.

## 4 Device Information

### 4.1 Investigational device description

The device under investigation in this study is the XprESS Multi-Sinus Dilation System (XprESS device). The device is currently a Class I, 510(k)-cleared, commercially available device for balloon sinus dilation.

The XprESS device combines features of a curved suction tip and an ostium seeker with the tissue expansion effect of balloon dilation. The features of this device enable a physician to track the device to the Eustachian tubes using endoscopic visualization. The distal end of the device is re-shapeable, allowing easy access to the Eustachian tubes. The XprESS curved suction tip has an atraumatic ball tip. A suction tube may be connected to the proximal barbed fitting to provide active suction by covering the suction vent. The XprESS balloon is available in diameters of 3-5 mm and in lengths of 8, 18, and 20 mm. All sizes are appropriate for treating Eustachian tubes; selection is based on physician preference. The XprESS device is provided sterile and for single use only.

### 4.2 Anticipated changes in device design

Changes to the device during the course of the IDE study are not anticipated. If such changes occur, Entellus Medical will inform investigators and will submit the appropriate supplemental applications to FDA, as necessary.

### 4.3 Investigational device management

Entellus Medical will control the use of the investigational devices by the following activities:

- Shipping or hand-carrying devices only to approved investigators who are participating in the study
- Maintaining records of shipment and distribution of the devices
- Maintaining records of devices used on subjects and returned devices

### 4.4 Device malfunctions

A device malfunction is defined as a failure of a device to meet its performance specifications or otherwise to perform as intended. A malfunction may be a result of any of the following: failure, malfunction, improper or inadequate design, manufacturing, labeling, or user error.

All device malfunctions must be reported on the Device Malfunction CRF. All attempts should be made to return malfunctioning devices to Entellus Medical for evaluation. Contact the clinical monitor for instructions on used device preparation and return procedures.

## 5 Monitoring Procedures

Entellus Medical personnel or qualified designees will monitor the clinical study in a manner consistent with 21 CFR 812, Subpart C, Responsibilities of Sponsor.

### 5.1 Name and address of the Lead Monitor

Clinical Monitor:     Robyn Schacherer  
                          Entellus Medical Inc.  
                          3600 Holly Lane North, Suite 40  
                          Plymouth, MN 55447  
                          Phone: (763) 463-7054  
                          Fax:   (763) 463-1599  
                          E-mail: [rschacherer@entellusmedical.com](mailto:rschacherer@entellusmedical.com)

Additional designated program monitors may be assigned and contact information provided separately.

### 5.2 Investigators

The clinical monitors will ensure investigators are selected based on their qualifications and ability to fulfill the investigator responsibilities. Investigator qualifications and responsibilities are outlined in the Investigator Agreement that each investigator must sign before enrolling subjects in the study. An updated list of investigators and Institutional Review Boards (IRBs) will be provided to the FDA every 6 months during the study, or as otherwise requested.

### 5.3 Investigational center monitoring

Monitoring visits to the investigational centers will be conducted frequently during the study to ensure that all aspects of the current approved protocol and any amendment(s) are followed. Source documents will be reviewed for verification with data on the CRFs and all regulatory documents will be checked for accuracy including but not limited to IRB approvals, study-related correspondence, and subject informed consent. The investigator and/or investigational center staff must be available to meet with the sponsor during monitoring visits.

Upon reasonable notice, the investigator and institution agree to provide the sponsor representatives or designees and applicable regulatory authorities with direct access to source documents relevant to the study for sponsor quality assurance audits or inspections by the regulatory authorities.

## 6 Adverse Event Definitions and Reporting

### 6.1 Adverse events

An adverse event (AE) is any undesirable clinical occurrence experienced by the subject during the follow-up period regardless of the event's relationship to either the study device or the procedure. An underlying disease that was present at the time of enrollment is not an AE; however, any increase in the severity of an underlying disease is an AE. All adverse events will be reported to FDA in annual progress reports.

Microtears (<5 mm) of the ET mucosa after balloon dilation in the absence of other undesirable effects are not considered adverse events. It is hypothesized that the microtears are related to the mechanism of action and are critical to the tissue healing and remodeling of the ET after balloon dilation.

### 6.2 Serious adverse events

A serious adverse event (SAE) is an event that results in any of the following:

- Death
- Life-threatening
- Hospitalization or prolongation of an existing hospitalization
- Invasive surgical intervention to correct or prevent further injury
- Persistent or significant disability or incapacity
- An important medical event

An important medical event that may not meet one of the above definitions might be considered as an SAE if it jeopardizes the health of the subject or requires surgical intervention to prevent one of the outcomes listed in the above definition. An example of an important medical event is postoperative bleeding that requires an intervention such as cautery or additional packing but does not require hospitalization.

An elective hospitalization/intervention that was planned before the subject enrolled in the study is not considered an SAE as defined above.

### 6.3 Unanticipated adverse device effects

As defined in the IDE regulation 21 CFR 812.3, an unanticipated adverse device effect (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 was not previously identified in nature, severity, or degree of incidence in the protocol, subject informed consent form, or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

### 6.4 Assessing, recording, and reporting AEs, SAEs, and UADEs

An AE may be volunteered spontaneously by the subject or discovered as a result of questioning or physical examination by the investigator or study staff. The following information should be

reported for all AEs as soon as the investigator becomes aware of the event and updated as needed until the event resolves:

- Date the AE occurred
- Date the investigator (or staff) became aware of the AE
- Description of the AE (main complaints or symptoms)
- Relationship to the study device
- Relationship to the study procedure
- Seriousness
- Interventions undertaken
- Status of the AE

Source documents (eg, procedural notes, treatment notes, clinical summary) may be required as supporting documentation for an AE, SAE, or UADE.

During the study, all subject deaths must be reported to the sponsor within 24 hours of the investigator's (or designated staff's) knowledge of the death. Deaths should be reported on the End of Study CRF and the event leading to the death reported on an AE CRF. A copy of death records, medical records for the event(s) that led to the subject's death, death certificate (if available), and an autopsy report (if performed) should be deidentified and sent to the sponsor as soon as they become available.

## 7 Protocol Deviations

Investigators are required to adhere to the study protocol, signed Investigator Agreement, applicable national or local laws and regulations, and any conditions required by the applicable IRB or regulatory authority.

A protocol deviation is used to describe situations in which the protocol was not followed (including all required activities at each scheduled visit or activities occurring outside of the study windows). All attempts should be made to obtain sponsor approval for deviations before their occurrence.

An investigator must notify the sponsor and the applicable IRB of any deviation from the study protocol done to protect the life or physical well-being of a subject (medical emergencies). Such notice should be given within 24 hours. The sponsor will determine if the subject affected is eligible to continue in the study.

Documentation of deviations identified by the investigational center, the monitor, or other sponsor representative(s) will be entered onto the Protocol Deviation CRF for the purpose of tracking compliance with the protocol. The investigational centers will be required to document actions taken to prevent recurrence of deviations. The sponsor representative will initiate corrective actions based on individual deviations or trending reports, as appropriate.

## 8 Labeling

Entellus Medical will modify the existing FDA-cleared labeling (package labels and IFU documents) for the XprESS device to include the required investigational device statement (below), the indication statement, risks, and treatment procedure specific to Eustachian tube dilation.

The following statement will be included on the outer packaging unit and the IFU as required by 21 CFR 812.5:

- CAUTION-Investigational Device. Limited by Federal (or United States) law to investigational use.

## 9 Administrative Information

### 9.1 Investigational center selection

The study will be conducted at up to 7 investigational centers in the US. Centers will be evaluated to ensure each center has the capacity and capability to obtain informed consent and comply with all protocol requirements. The investigators and investigational center personnel are required to comply with the principles of Good Clinical Practices (GCP) as described in the FDA regulations.

### 9.2 Training

The training of investigational center personnel will be the responsibility of the sponsor or sponsor-authorized representatives. All treating physicians must be proficient in the use of endoscopic techniques. All physicians will be trained on the preparation and use of the XprESS device before subject enrollment in this study.

To insure uniform data collection and protocol compliance, the sponsor or sponsor-authorized representatives will review all components of the study with the study coordinator(s)/study staff at each investigational center. The review will include the study protocol, techniques for the identification of eligible patients, instructions for data collection during the procedure, and schedules for follow-up.

### 9.3 Informed consent process

Informed consent must be obtained in accordance with US regulation 21 CFR 50. The subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and also informed that withdrawal from the study will not jeopardize their future medical care. The standard institutional patient consent form does not replace the study informed consent form (ICF).

The sponsor will provide a study-specific ICF template to each investigational center for IRB submission. This template may be modified to suit the requirements of the individual investigational center. The sponsor must preapprove all changes to the ICF before initial submission to the IRB. The IRB-approved consent form must be sent to and approved by the sponsor before the first device shipment. One approved copy must be retained in the investigational center's study files along with the other investigational forms.

Each enrolled subject must be given a copy of their signed consent form and another copy must be retained in the investigational center study file for that subject. Informed consent documents must be available for review by the sponsor during monitoring visits.

Modifications to the study-specific ICF and/or any other written information distributed to subjects must be preapproved by the sponsor and the IRB, as necessary.

#### 9.4 Confidentiality

All information and data sent to the sponsor concerning subjects or their participation in this study will be considered confidential. Subjects will be identified by a study-specific identification code. All data used in the analysis and reporting of this investigation will use the study-specific codes and will not include identifiable references to individual subjects. Any source documentation must be deidentified by the investigational center before being sent to the sponsor.

The investigator will allow visits by the sponsor representatives and the US FDA inspectors or any other local governmental body to review the study subjects' medical records, including test or laboratory data that might have been recorded on diagnostic test media (eg, CT scan).

#### 9.5 Institutional Review Board (IRB)

It is the investigator's responsibility to obtain and maintain written approval of the final investigational plan and ICF from the applicable IRB. The investigator is responsible for submitting and obtaining initial and continuing review of the study by the IRB. It is also the investigator's responsibility to notify the IRB of any amendments to these documents. Written IRB approval must identify the study by title and version, document the date of review, and be forwarded to the sponsor before the first device shipment.

The investigator must keep all study-related correspondence with the IRB on file and forward copies of such correspondence to the sponsor.

#### 9.6 Investigator responsibilities

The investigator for each investigational center is responsible for ensuring the study is conducted according to:

- All signed agreements
- The study protocol
- IRB guidelines
- Applicable local and federal regulations

The investigator for each center may not begin enrollment until the sponsor receives and approves (when necessary) required documents, including the signed Investigator Agreement and the IRB approvals of the investigational plan and ICF.

It is acceptable for the investigator to delegate 1 or more of the above functions to a subinvestigator or trained study coordinator; however, the investigator remains responsible for the proper conduct of the clinical investigation, including obtaining informed consent, collecting all required data, and submitting accurate and complete CRFs.

At each investigational center, appropriate procedures must be followed to maintain subject confidentiality according to HIPAA (Health Insurance Portability and Accountability Act) regulations. Each center may have its own internal procedures or requirements for use and release of subject medical information in research studies. Each investigator is responsible for

obtaining appropriate approvals, consents, or releases of medical information as dictated by their relevant patient privacy laws.

The study is not transferable to other centers/facilities attended by the investigator unless preapproval is obtained from the applicable IRB and the sponsor.

### 9.7 Sponsor responsibilities

The sponsor's responsibilities for this study are to:

- Provide sufficient training to participating investigational centers to support study activities according to the agreements executed with the centers
- Select all clinical investigators and investigational centers and other consultants (eg, the study monitors) who participate in the study
- Provide financial support to each center according to the agreements executed with each center
- Follow/promote all regulatory standards according to local/federal regulations for the investigational centers, core laboratories, and other participants, and ensure regular investigational center monitoring to assure compliance with the regulations
- Retain ownership of all clinical data generated in this study and control the use of the data for appropriate purposes only
- Review and approve publication of study results in the literature
- Ensure timely and appropriate study registration in a public clinical trial database (eg, Clinicaltrials.gov), if applicable

### 9.8 Criteria for terminating study

The sponsor reserves the right to terminate the study early but intends only to exercise this right for valid scientific or administrative reasons or reasons related to the protection of study subjects. Investigators, applicable IRBs, and FDA will be notified in writing in the event of study termination. Reasons for study termination include but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the study subjects
- A decision on the part of the sponsor to suspend or discontinue commercial distribution of the device

### 9.9 Criteria for terminating an investigational center

The sponsor reserves the right to stop enrollment of subjects at a particular investigational center at any time after the study initiation visit for any of the following reasons:

- Repeated failure to complete CRFs in a timely manner
- Failure to obtain appropriate informed consent
- Failure to report any study subject deaths, SAEs, or UADEs within the timeframes specified in Table 3
- Loss of or unaccounted product inventory
- Repeated protocol deviations
- Lack of study enrollment or study activity

## 10 Reports and Records

### 10.1 Records

In accordance with 21 CFR 812.140(d), all records pertaining to the clinical study will be kept for a minimum of 2 years following the date on which the study is terminated or completed. If an investigator wishes to withdraw from the responsibility of maintaining these study records, a transfer of that responsibility to a person willing to accept the responsibility (as outlined in 21 CFR 812.140) must occur and be reported to the sponsor not more than 10 days after the transfer occurs.

### 10.2 Reporting requirements

**Table 3** shows a summary of all investigator reporting requirements. In addition to this list, individual IRBs may add additional reporting requirements and/or require a different notification time frame. The principal investigator at each investigational center is responsible for ensuring any additional local IRB reporting requirements are met.

Table 3. Summary of Investigator Reporting Requirements

Type of report	Prepared by Investigator for:	Notification time frame
Unanticipated Adverse Device Effect (UADE)	Sponsor & IRB	Within 10 working days of knowledge
Failure to obtain informed consent prior to device use	Sponsor & IRB	Within 5 working days
Withdrawal of IRB approval	Sponsor	Within 5 working days of knowledge
Subject withdrawal	Sponsor	Within 10 working days of knowledge
Final report	Sponsor & IRB	Within 3 months after completion or termination
Progress report	Sponsor & IRB	At minimum annually
Deviations due to emergency	Sponsor & IRB	Within 5 working days of emergency

**Table 4** lists the sponsor reporting requirements and notification time frames.

Table 4. Summary of Sponsor Reporting Requirements

<b>Type of report</b>	<b>Prepared by Sponsor for:</b>	<b>Notification time frame</b>
Unanticipated Adverse Device Effect (UADE)	FDA	Within 10 working days of receipt
Failure to obtain informed consent prior to device use	FDA	Within 5 working days of receipt
Withdrawal of IRB approval	FDA	Within 5 working days of receipt
Withdrawal of FDA approval	Investigators & IRB	Within 5 working days of receipt
Recalls and device disposition	FDA & IRB	Within 30 working days after request
Final report	FDA, IRB, & Investigators	6 months after completion or termination of study
Progress reports	FDA & IRB	Annually
Current investigator list	FDA	6 month intervals after FDA approval
Study completion or termination	FDA	Within 30 days of completion or termination

## 11 References

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- <sup>1</sup> Seibert JW, Danner CJ. Eustachian tube function and the middle ear. *Otolaryngol Clin N Am.* 2006;39:1221-1235.
- <sup>2</sup> Bluestone CD. *Eustachian Tube: Structure, Function, Role in Otitis Media.* Hamilton, Ontario, Canada: BC Decker, Inc.; 2005.
- <sup>3</sup> Poe DS, Hanna BMN. Balloon dilation of the cartilaginous portion of the eustachian tube: initial safety and feasibility analysis in a cadaver model. *Am J Otolaryngol.* 2011;32:115-123.