

**DE NOVO CLASSIFICATION REQUEST FOR
ACCLARENT AERA™ EUSTACHIAN TUBE BALLOON DILATION SYSTEM**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Eustachian Tube Balloon Dilation System. A Eustachian tube balloon dilation system is a prescription device that includes a flexible catheter attached to an inflatable balloon. The system is intended for use in dilating the cartilaginous portion of the Eustachian tube for treating persistent Eustachian tube dysfunction.

NEW REGULATION NUMBER: 874.4180

CLASSIFICATION: CLASS II

PRODUCT CODE: PNZ

BACKGROUND

DEVICE NAME: ACCLARENT AERA™ EUSTACHIAN TUBE BALLOON DILATION SYSTEM

SUBMISSION NUMBER: DEN150056

DATE OF DE NOVO: DECEMBER 4, 2015

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INDICATIONS FOR USE

The ACCLARENT AERA™ Eustachian Tube Balloon Dilation System is intended to dilate the Eustachian tube for treatment of persistent Eustachian tube dysfunction in adults ages 22 and older.

LIMITATIONS

The sale, distribution, and use of the ACCLARENT AERA™ Eustachian Tube Balloon Dilation System are restricted to prescription use in accordance with 21 CFR 801.109.

Limitations on device use are also achieved through the following contraindications, warnings, and precautions included in the Instructions for Use:

CONTRAINDICATIONS

The ACCLARENT AERA™ Eustachian Tube Balloon Catheter is contraindicated for use in a Eustachian tube with an ipsilateral carotid artery that is dehiscant into the ET lumen or history of ipsilateral patulous Eustachian tube.

WARNINGS

- Intended for single patient use only. **DO NOT REUSE.**
- Patients with a history of skull base surgery, prior ear surgery, skull fracture, or anatomic abnormalities may have elevated risk of complications and should be radiographically screened for eligibility before treatment.
- DO NOT use product if the integrity of the sterile packaging has been compromised or if the device appears damaged.
- DO NOT use the ACCLARENT AERA™ Eustachian Tube Balloon Catheter if the device becomes damaged or touches a non-sterile object outside of the operating field.
- Never advance or retract the device against unknown resistance, as this could cause tissue trauma or device damage.
- Advancing the Eustachian Tube Balloon Catheter into the Eustachian tube against resistance may cause injury.
- DO NOT exceed the recommended maximum balloon inflation pressure of 12 atmospheres (ATM).
- Use only sterile saline or sterile water for inflation. DO NOT inflate with air.
- The safety of the device as used under local anesthesia has not been evaluated.

PRECAUTIONS

- DO NOT move the balloon while it is inflated. Ensure balloon is fully deflated during insertion and withdrawal.
- Radiographic assessment of the targeted Eustachian tube is recommended prior to any procedure involving balloon tuboplasty.
- Certain nasal anatomy such as a deviated nasal septum may preclude access to the Eustachian tube/s resulting in failure to treat the target anatomy.
- DO NOT inflate the Eustachian Tube Balloon Catheter until it has exited the ACCLARENT AERA™ Eustachian Tube Guide Catheter.
- DO NOT bend the Guide Catheter shaft.

DEVICE DESCRIPTION

The ACCLARENT® AERA™ Eustachian Tube Balloon Dilation System includes the Eustachian Tube Balloon Catheter (ETBC) and the Eustachian Tube Guide Catheter (ETGC). The system is provided with the following additional devices: the Acclarent SE Inflation Device (or Acclarent Balloon Inflation Device) and Relieva Extension Tubing. The Acclarent SE Inflation Device (or Acclarent Balloon Inflation Device) is used to inflate the ETBC. The Acclarent SE Inflation Device and Acclarent Balloon Inflation Device are FDA cleared devices (K150172 and K052198, respectively). The Relieva Extension Tubing may be used to connect the Balloon Catheters and the Inflation Device when additional tubing length is required. The

Relieva Extension Tubing is a Class I exempt device under 21 CFR 874.4420. All devices are provided sterile for single-patient use.

The ETBC is a 6x16mm (inflated diameter x length) flexible Balloon Catheter (Figure 1) with an integrated shaft and a nylon balloon at the distal tip. The non-compliant balloon is designed to dilate the cartilaginous portion of the Eustachian tube (ET). The shaft consists of dual lumen tubing with an actuator component that is designed to assist in rotation and advancement of the ETBC. The beaded catheter tip (aka, “blueberry tip”) on the ETBC is designed to restrict advancement of the device into the bony portion of the ET, known as the isthmus. There is an endoscopic marker placed at the proximal taper of the balloon to aid in positioning under direct endoscopic visualization.

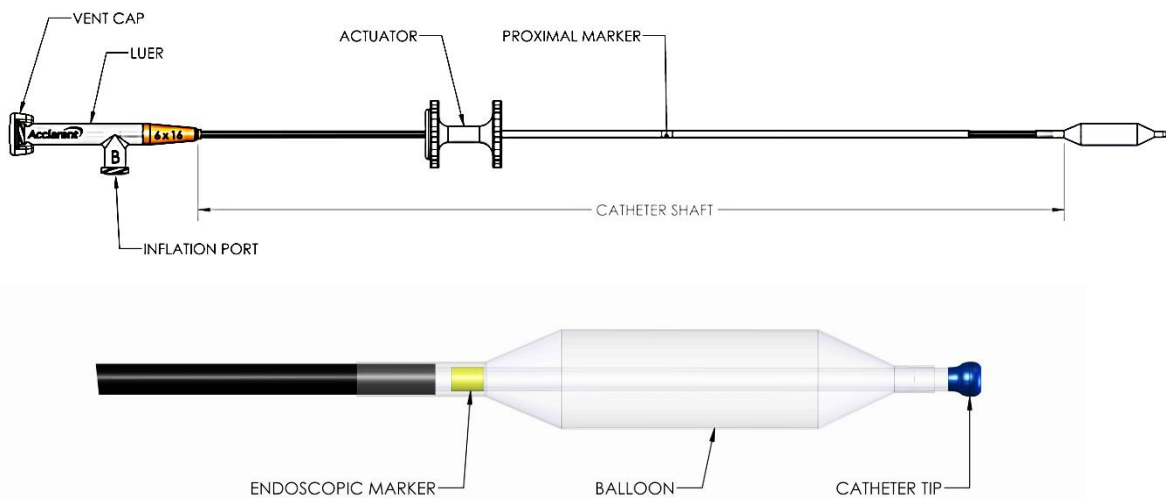


Figure 1: Illustration of the Eustachian Tube Balloon Catheter

The ETGC (Figure 2) is designed to facilitate ETBC access to the ET. The ETGC incorporates an atraumatic distal tip and distal angled tip profile that facilitates access to the ET. The ETGC contains a lubricious inner liner to allow smooth passage for the ETBC and includes a hypotube for rigidity.

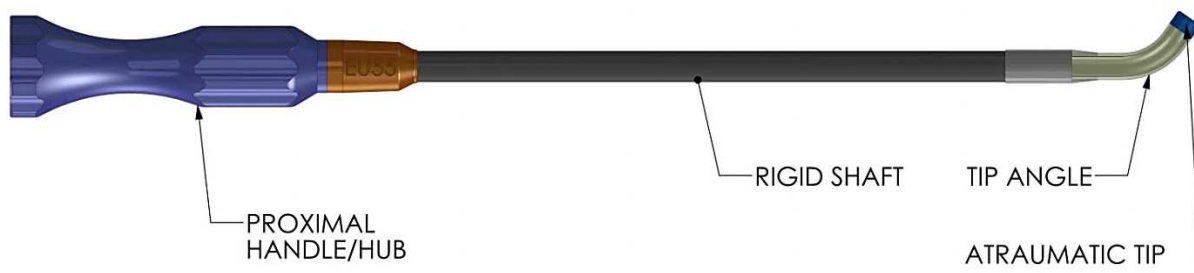


Figure 2: Diagram of Eustachian Tube Guide Catheter

SUMMARY OF NONCLINICAL/BENCH STUDIES

The ACCLARENT® AERA™ Eustachian Tube Balloon Dilation System was tested to ensure that it functions according to the design specifications. The device passed the following nonclinical tests as described below.

BIOCOMPATIBILITY/MATERIALS

The materials used in the ACCLARENT® AERA™ Eustachian Tube Balloon Dilation System are well known and commonly used in the medical device industry, and are appropriate for ethylene oxide (EO) sterilization.

Both the Balloon Catheter and Guide Catheter are considered surface-contacting devices that contact breached or compromised surfaces for limited duration (less than 24 hours) according to ISO 10993-1: 2009/Corr 1:2010. The patient contacting materials including the adhesives were evaluated for cytotoxicity, sensitization, irritation, and acute systemic toxicity per ISO 10993-1, and FDA Bluebook Memorandum G95-1 entitled “Required Biocompatibility Training and Testing Profiles for Evaluation of Medical Devices,” as listed in Table 1: Biocompatibility Testing Table 1. The results of these tests were found to be acceptable.

Table 1: Biocompatibility Testing

Test Name	Test Method	Results
Biocompatibility – Balloon Catheter and Guide Catheter		
Cytotoxicity	ISO 10993-5:2009 Biological Evaluation of Medical Devices: Tests for Cytotoxicity: <i>in vitro</i> ; MEM Elution method	Acceptable
Sensitization	ISO 10993-10:2010: Biological Evaluation of Medical Devices: Tests for Irritation and Delayed Type Hypersensitivity: Guinea Pig Maximization Sensitization method	Acceptable
Irritation	ISO 10993-10:2010: Biological Evaluation of Medical Devices: Tests for Irritation and Sensitization: Rabbit Intracutaneous method	Acceptable
Acute Systemic Toxicity	ISO 10993-11:2006: Biological Evaluation of Medical Devices: Tests for Systemic Toxicity	Acceptable

SHELF LIFE/STERILITY

Packaging, shelf life and sterilization testing is summarized in Table 2. The ETBC and the ETGC are packaged together on a b(4) CCI backer card in a b(4) CCI pouch. The pouches are then placed into cartons and sterilized using ethylene oxide (EO). The validation of this sterilization process complies with ISO 11135:2014—“Sterilization of Health Care Products—Ethylene Oxide: Requirements for Development, Validation, and Routine Control of a Sterilization Process for Medical Devices”. The sterilization method achieves a sterilization assurance level (SAL) of 10⁻⁶.

The proposed shelf life of 2 years has been validated using accelerated aging. The accelerated aging testing was conducted according to ASTM F1980-07; followed by testing on the packaging configuration and functional performance. Seal strength testing was conducted according to ASTM F88-09, and whole package integrity was conducted according to ASTM F2096-11. Real time aging for 2 years has been initiated and will be followed by the same testing on the packaging configuration and functional performance to confirm the proposed shelf life.

Transit testing was performed on the ACCLARENT® AERA™ Eustachian Tube Balloon Dilation System after EO sterilization, climate conditioning per ISO 2233:2000 and transit simulations (compression, initial random vibrations, impact, and final random vibration) per ASTM D4169:2009.

Table 2: Sterilization, Shelf Life and Packaging Testing

Test Name	Test Method	Acceptance Criteria	Results
Sterilization – Balloon Catheter and Guide Catheter			
Sterilization Validation	ISO 11135:2014: Sterilization of health-care products - Ethylene oxide - Requirements for the development, validation and routine control of a sterilization process for medical devices	Sterility assurance level (SAL) of 10 ⁻⁶	Passed
Ethylene Oxide Residuals	ISO 10993-7:2008: Biological Evaluation of Medical Devices: Ethylene oxide sterilization residuals	Ethylene oxide (EO) ^{b(4)} device and Ethylene chlorohydrin (ECH) ^{b(4)} mg/device	Passed
Shelf Life and Packaging – Balloon Catheter and Guide Catheter			
Environmental Conditioning	ISO 2233:2000: Packaging - Complete, filled transport packages and unit loads - Conditioning for testing	N/A	Completed
Transportation Simulation	ASTM D4169:2014: Standard Practice for Performance Testing of Shipping Containers and Systems	Testing performed for compression, initial random vibrations, impact, and final random vibration	Completed

Test Name	Test Method	Acceptance Criteria	Results
Accelerated Aging	ASTM F1980-07: Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices	Testing to simulate shelf life of 2 years	Completed
Package Integrity (Visual)	ASTM F1886/F1886M: Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection	<ul style="list-style-type: none"> • No damage to package (pouch or box) that could affect product performance, marketability, or sterility after compression, vibration, and drop challenges. • Package shall have no damage, defects/smudges to the pouch labeling. • The device shall stay in the intended place during compression, vibration, and drop challenges. • Minimum seal width of 1/4" 	Passed
Gross Leak Detection	ASTM F2096-11: Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test)	No gross leak	Passed
Seal Strength	ASTM F88-09: Standard Test Method for Seal Strength of Flexible Barrier Materials	b(4) CCI minimum for individual value and b(4) CCI minimum for the average value	Passed

PERFORMANCE TESTING – BENCH

Functional testing was performed on both the ETBC and the ETGC, as summarized in Table 3 **Error! Reference source not found.** The testing was performed on devices after EO sterilization, environmental conditioning, transit simulations, and accelerated aging, to simulate worst-case conditions. All testing was performed with a compatible inflation device. The devices passed all functional testing.

Table 3: Performance Testing

Test Name	Test Method	Acceptance Criteria	Results
Performance Testing - Balloon Catheter			
Dimensional	Measure the dimensions of the catheter, balloon, location and dimensions of the yellow endoscopic marker, proximal shaft marker, flexible length of the balloon catheter, balloon bond, tip and venting lumen	Per device design specifications	Passed
Deflation time	Verify the time to deflate the balloon	Deflation time b(4) CCI	Passed
Balloon Burst Pressure	Evaluate that the balloon does not burst when subjected to the maximum rated pressure	Pressure > b(4) CCI	Passed
Tensile Strength	Evaluate the tensile strength of all joints	Force at break b(4) CCI	Passed
Balloon Catheter Tip Test	Ensure that balloon catheter tip is bonded securely by evaluating its tensile strength	Force at break b(4) CCI	Passed
Insertion/Retraction Test	Ensure that balloon catheter can withstand multiple insertion/retraction cycles through the Guide Catheter without structural damage or balloon leakage	After 4 insertion/retractions	Passed
Fatigue Test	Ensure that the balloon can withstand multiple inflation/deflation cycles at the maximum rated pressure	8 cycles @ b(4) CCI	Passed
Label	Visually verify that correct label is applied to the balloon and balloon inflation port label	Visual confirmation	Passed
Performance Testing - Guide Catheter			
Dimensional	Measure the dimensions of the catheter, distal tip, and transition bond	Per device design specifications	Passed

Test Name	Test Method	Acceptance Criteria	Results
Fatigue	Ensure that the catheter can withstand multiple insertion/retraction cycles of the balloon catheter through it	After 4 insertion/retraction cycles	Passed
Materials	Ensure that the materials used to construct distal shaft are clear/ translucent so that balloon catheter tip and yellow endoscopic marker are visible in the guide distal shaft during insertion	Visual confirmation	Passed
Torque	Test the torque resistance to ensure no material or joint failure	Torque \geq b(4) CCI	Passed
Tensile Strength	Evaluate the tensile strength of all joints	Force at break \geq b(4) CCI	Passed
Label	Visually verify that the correct label is applied on the guide handle	Visual confirmation	Passed

PERFORMANCE TESTING – CADAVER

The ACCLARENT® AERA™ Eustachian Tube Balloon Dilation System was evaluated in cadavers to ensure that it functions in accordance with its design specifications and intended use. This simulated use testing was conducted by ENT physicians using cadaveric specimens.

Each evaluator used the same device to dilate a left and a right ET of the same specimen. Evaluators were asked to assess various attributes such as device placement without excessive advancement to the bony portion of the ET, ability to attach the compatible inflation device or extension tubing to the ETBC, ETBC movement through the ETGC, ability to position and operate the system with one hand, ability to avoid unacceptable trauma to mucosa or anatomical structures, and ability to maintain device functionality throughout treatment. The acceptance criteria for this study were a clinically acceptable rating of “2” or higher on a 1-4 point scale, with 4 defined as “excellent” performance and 1 defined as “clinically unacceptable” performance.

All ratings from each evaluator were above “2”. Therefore all performance requirements met the acceptance criteria. The lowest average rating for each requirement was 3.3, while the highest average rating was 3.7 out of a possible rating of 4. The system performed as intended and no safety issues were observed.

SUMMARY OF CLINICAL INFORMATION

Introduction: Acclarent designed and executed a randomized controlled study evaluating the safety and efficacy of the subject device with the goal of providing sufficient evidence to support a reasonable assurance of safety and efficacy.

Study Objectives: To evaluate efficacy and safety of ET balloon dilation with the Eustachian Tube Balloon Catheter (ETBC) in conjunction with medical management (investigational arm) compared to medical management alone to treat Eustachian tube dysfunction (ETD) in adult patients (control arm).

- Primary efficacy endpoint evaluation consists of comparison of the proportion of subjects experiencing normalization of tympanometry at 6 weeks post-treatment in the investigational arm versus the proportion of subjects experiencing normalization of tympanometry at 6 weeks post-randomization in the control arm.
- Secondary efficacy endpoint evaluation employs the Eustachian Tube Dysfunction Questionnaire (ETDQ-7) to compare the proportion of subjects achieving at least a minimally important difference (MID) level improvement of 0.5 points at 6 weeks post-treatment in the investigational arm versus the proportion of subjects achieving at least a MID level improvement of 0.5 points at 6 weeks post-randomization in the control arm.
- Safety evaluation includes occurrence of all anticipated or unanticipated adverse events in both treatment arms.

Study Methodology: The study was a prospective, multi-center, randomized controlled trial to demonstrate superiority of the ET balloon dilation with ETBC in conjunction with medical management (investigational arm) compared to medical management (MM) alone (control arm) to treat ETD. Study population includes subjects age 22 and older with ETD refractory to medical therapy. Each investigator was required to perform 3 successful ETBC procedures in non-randomized Lead-In subjects. MM consists of treatment with triamcinolone acetonide (TA) nasal steroid spray (such as Nasacort® AQ Nasal Spray (NAQ) or equivalent). All enrolled study subjects in both the lead-in and randomized phase are required to adhere to the recommended TA labeling dosage and frequency through the 6 week follow-up visit. All ETBC procedures were performed under general anesthesia in the operating room.

The randomized cohort is conducted in a 2:1 ratio with two subjects randomized to ETBC for every one MM subject. The study is a group sequential design with 3 planned looks (2 interim and 1 final) at 54:27, 108:54, and 162:81 evaluable subjects. The clinical evidence being presented in this summary is supported by the second-look cohort.

The primary endpoint was graded by both the investigator as well as an independent evaluator with appropriate expertise unaffiliated with study patient care. The independent tympanogram evaluator was blinded to subjects' arm assignment and had no knowledge of the outcome of the investigators' tympanogram results.

Each subject was enrolled individually and served as the unit of analysis, regardless of indication for unilateral or bilateral ETD. Subjects had five follow-up visits. Follow-up visits occurred at 2

weeks, 6 weeks, 12 weeks, 24 weeks, and 52 weeks following either randomization (control arm) or the ETBC procedure (investigational arm). MM subjects may cross over to receive an ETBC procedure after the 6 week follow-up visit and are subsequently followed for 12 weeks post-procedure.

Number of Subjects (planned and analyzed): The second interim analysis cohort consisted of 72 MM, 141 ETBC and 81 enrolled Lead-In subjects. Twenty-one (70) MM subjects crossed over to receive an ET dilation procedure and are included in the safety analysis of 299 subjects (80 lead-in + 149 randomized ETBC + 70 MM cross-overs).

Diagnosis and Main Criteria for Inclusion: The study includes adult males or females aged 22 years and older diagnosed with persistent ETD. Persistent ETD is defined by patient-reported symptoms of ETD (including pressure and/or pain and/or clogged and/or muffled sensation in the affected ear(s)) and documented evidence that the subject has experienced persistent ETD symptoms for 12 weeks or greater prior to enrollment. Patients must have failed appropriate medical management consisting of either a minimum of 4 weeks of continuous daily usage of any intranasal steroid spray (INS) or a minimum of one completed course of an oral steroid. The failed medical management may occur any time within 90 days prior to study enrollment. In addition, all patients are required to have a computed tomography (CT) scan taken to confirm absence of internal carotid artery (ICA) dehiscence into the Eustachian tube (ET) lumen bilaterally.

All patients must present with abnormal tympanometry (type B or type C) after failed MM and within 14 days prior to study enrollment. In addition, all included patients must have demonstrated symptomatic dysfunction as documented through a validated quality of life instruments (the ETDQ-7) with a score ≥ 2.1 after failed MM.

Females who are pregnant or lactating were excluded. In addition subjects were excluded if they had (1) anatomy that required an adjunctive surgical procedure on the same day as ETBC surgery to allow balloon catheter access to the ET, or (2) concomitant nasal, sinus or ear procedures planned on the same day as ETBC surgery or any time during study participation. This criterion did not apply to Lead-In subjects. In addition, patients were excluded if they have a history of major surgery of the head or neck within four (4) months prior to randomization, patulous ET in either ear, fluctuating sensorineural hearing loss, active chronic or acute otitis media (AOM), tympanic membrane perforation or presence of a tympanostomy tube in either ear, tympanosclerosis, acute upper respiratory infection, active temporomandibular joint disorder (TMJ), cleft palate or history of cleft palate repair, craniofacial syndrome, cystic fibrosis, ciliary dysmotility syndrome, systemic mucosal diseases or immunodeficiency disorders, intolerance of protocol-defined medication regimen, prior surgical intervention on ET, or absence of dilatory muscular contractions.

EFFICACY RESULTS:

Technical success was high with 298/299 (99.7%) of all targeted ETs successfully accessed and dilated. The one (1) failure was due to anatomical constraint undetected prior to procedure, resulting from angiofibroma surgery 31 years prior which prevented appropriate balloon access

and positioning. Several events considered as device malfunctions were reported. Two (2) ETBC were reported to have leaked saline upon inflation; of these, one (1) device was disposed following the procedure and was not returned to the company for testing; one (1) device was returned for testing which indicated a functional balloon (i.e., the leak was not confirmed). One (1) ETBC was bent during approach into the ET. No adverse events were associated with the malfunctions.

Primary efficacy results demonstrated superiority of the investigational device plus MM compared to MM alone. Tympanogram normalization was observed in 51.8% (73/141) of investigational subjects compared to 13.9% (10/72) controls ($p < 0.0001$). The Fisher's exact p-value for the 2nd planned look was smaller than the pre-planned O'Brien-Fleming stopping p-value at 0.00706. As the primary endpoint did meet the early stopping criteria, enrollment in the study has been ceased. Sensitivity analysis was performed to test the robustness of efficacy results and the impact of missing data in the intent-to-treat (ITT) cohort compared to the primary analysis cohort (PAC). Sensitivity analysis results suggest there is not a large source of uncertainty in the outcomes interpretation since no tipping point was identified.

The data demonstrated a degree of site variation with regards to the treatment effect at the primary endpoint at 6 weeks, which is summarized in Table 4.

Table 4: Primary Endpoint Achievement at 6 weeks

Site	Randomized ETBC (N = 141 Subjects at Baseline)	Medical Management (N = 72 Subjects at Baseline)	Total # of Subjects
1	78.9% (15/19)	18.2% (2/11)	30
2	33.3% (6/18)	0.0% (0/9)	27
3	29.4% (5/17)	30.0% (3/10)	27
4	57.1% (8/14)	0.0% (0/9)	23
5	91.7% (11/12)	0.0% (0/6)	18
6	60.0% (6/10)	50.0% (3/6)	16
7	0.0% (0/9)	25.0% (1/4)	13
8	77.8% (7/9)	0.0% (0/4)	13
9	33.3% (2/6)	25.0% (1/4)	10
10*	62.5% (5/8)	0.0% (0/1)	9
11	50.0% (3/6)	0.0% (0/2)	8
12	40.0% (2/5)	0.0% (0/2)	7
13**	50.0% (2/4)	0.0% (0/2)	6
14	25.0% (1/4)	0.0% (0/2)	6

* Data from 5 pooled sites

** Data from 2 pooled sites

The significant treatment by site interaction is believed to be consequence of two sites having a higher percentage of tympanogram normalization for MM subjects than for ETBC subjects (Investigator Sites 3 and 7). However, the results for these sites are inconsistent with the results from all other sites, which show a higher percentage of tympanogram normalization for ETBC

subjects. Possible explanations for the treatment by site interaction could include device and procedural learning curve of the investigators, subject and/or site conformance to the protocol, or statistical variance.

For the secondary efficacy endpoint, a greater proportion of subjects in the investigational arm achieved an MID level change for ETDQ-7 at 6 weeks compared to control. MID level change was observed for 90.6% (126/139) of investigational subjects compared to 45.1% (32/71) controls.

Subjects in the investigational arm (ETBC) also showed a greater improvement in ETDQ-7 score at 6 weeks compared to control (MM). Investigational subjects reported a -2.3 (1.4) mean (SD) improvement in ETDQ-7 score at 6 weeks compared to -0.5 (1.2) for control subjects. Additionally, a greater proportion of subjects in the investigational arm (ETBC) presented without symptomatic dysfunction at 6 weeks compared to control (medical management). Fifty-six percent point one percent (56.1%, 78/139) of investigational subjects reported an ETDQ-7 mean item score of less than 2.1 at 6 weeks compared to 8.5% (6/71) for control subjects.

Durability of treatment effect is supported by sustained outcomes for over 170 subjects, where 62.2% (61/98) randomized ETBC and 58.1% (43/74) lead-in subjects demonstrated tympanogram normalization at 24 weeks post-procedure compared to 51.8% (73/141) and 40.0% (30/75) at 6 weeks, respectively. Durability was consistently demonstrated across efficacy outcome measures where improvement in ETDQ-7 scores, proportion of subjects achieving a MID level improvement, and proportion of subjects without symptomatic dysfunction are sustained at 24 weeks post-procedure. Altogether, the efficacy results are supportive of greater improved outcomes for ETBC-treated patients compared to control and a durable treatment effect.

SAFETY RESULTS

In 444 dilated Eustachian tubes (299 subjects), 0 serious device- or procedure-related adverse events were reported. Sixteen (16) non-serious device or procedure-related adverse events occurred in 13 subjects out of the 299 subjects who underwent Eustachian tube dilation, including 4 events related to the anesthesia component of the procedure. Related events included those identified as “definitely related”, “probably related” and “possibly related”. A conservative approach was taken and events of “unknown relatedness” were also included.

All potentially device- or procedure-related events were not serious, mild or moderate in severity and resolved without sequelae with the most significant treatment interventions consisting of tympanostomy tube placements for 3 subjects or Tylenol for 1 subject.

LABELING

The labeling includes the Instructions for Use, which includes the device indications for use, a description of the device, contraindications, warnings and precautions, clinical data on the device, and instructions for the safe and effective use of the device. The labeling satisfies the

requirements of 21 CFR 801.109 Prescription devices.

The Instructions for Use addresses the known hazards and risks of the device for the intended use and incorporates safety statements to mitigate these risks, and instructions for how to prevent misuse of the device. The instructions also include information regarding compatibility and selection of appropriate products that can be used with the device, information about the shelf life, and information about the technical parameters such as the maximum allowed inflation pressure, geometry and available balloon sizes. In addition, the instructions provides a summary of the data on safety and effectiveness of the device from the randomized controlled trial comparing balloon dilation plus medical management vs. ongoing medical management alone.

RISKS TO HEALTH

Table 5 identifies the risks to health that may be associated with use of the Eustachian Tube Balloon Dilation System and the measures necessary to mitigate these risks.

Table 5: Identified Risks and Mitigation Measures

Identified Risk	Mitigation Measure
Introduction of false passages and rupture or damage to carotid artery	Non-clinical performance testing Simulated use testing Training Labeling
Injury to mucosal tissue <ul style="list-style-type: none"> • due to misuse of device on patulous Eustachian tube or following skull base surgery • due to catheter mechanical failure • due to balloon rupture • due to mishandling of device with respect to excessive force and/or incorrect positioning 	Non-clinical performance testing Simulated use testing Shelf life validation Training Labeling
Adverse tissue reaction	Biocompatibility evaluation
Infection	Sterilization validation Shelf life validation Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the Acclarent Aera™ Eustachian Tube Balloon Dilation System is subject to the following special controls:

1. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be evaluated:
 - a. Mechanical testing, including tensile and flexural testing of catheter joints and materials.

- b. Durability testing, including fatigue and burst pressure testing of the balloon materials and components.
 - c. Inflation and deflation characterization testing, including time and pressure measurements, and leak testing of the balloon.
 - d. Verification testing of safety features built into the device must be performed, including the characterization of catheter geometries and distal tip insertion limitation mechanisms.
2. Simulated use testing in a clinically relevant model must demonstrate the reliability of the device to remain mechanically functional throughout the anticipated conditions of use, and validate that the design features limit access to only the cartilaginous portion of the Eustachian tube.
3. The patient-contacting components of the device must be demonstrated to be biocompatible.
4. Performance data must demonstrate the sterility of the device.
5. Performance data must support shelf life by demonstrating continued sterility of the device, package integrity and device functionality over the identified shelf life.
6. Training must include simulated use on cadavers to ensure users can follow the instructions for use to allow safe use of the device.
7. Labeling must include:
 - a. Detailed instructions for use.
 - b. A detailed summary of the device technical parameters, including maximum allowed inflation pressure, allowable catheter geometries, and available balloon sizes.
 - c. A shelf life.

BENEFIT/RISK DETERMINATION

Persistent Eustachian Tube Dysfunction (ETD) can significantly degrade quality of life. Current standard of care such as medication and tympanostomy tubes have not been known to be universally effective or durable. Eustachian tube (ET) dilation using the ACCLARENT AERA™ Eustachian Tube Balloon Dilation System is proposed to be a less invasive technique for treating ETD than treatments such as ablation of mucosa and cartilage. ET dilation may help to relieve symptoms of ETD and sustain benefit of treatment over longer period of time. Patients might perceive these advantages as beneficial and may consider this as safe alternative treatment to other techniques.

The risks of the device are based on nonclinical laboratory and cadaver studies, as well as data collected in a clinical study described above. Probable serious adverse events related to the use of the device or the dilation procedure includes the introduction of false passages and rupture of the internal carotid artery (ICA), which lies immediately adjacent to the ET. Rupture of the

internal carotid artery can lead to excessive bleeding, stroke, and death from fatal bleeding which is near impossible to control in this location. This life-threatening risk is of particular concern in a patient with dehiscence of the bony carotid canal adjacent to the ET. Since the ICA is located close to the ET near the bony isthmus, and because the balloon dilation procedure using the device is visualized only in the nasopharynx and not at the distal end of the ET, the device could damage the bony canal and could lead to catastrophic complications resulting from injury to ICA. In addition, regardless of improvements in visualization with endoscopic approaches, the risk of injury to the ICA and associated severe complications remain, as supported by complications noted in early experience with peritubular ET injections for treatment of patulous ET as well as lateral skull base surgery. Probable device related and/or procedure-related non-serious adverse events include mucosal tears, minor bleeding, conductive deafness, epistaxis, and chronic otitis media.

To mitigate the risk of ICA rupture, the device specifically incorporates an enlarged, soft, distal tip designed to limit dilation to the distal cartilaginous portion of the ET, and physicians received training on the proper usage of the device on lead-in patients for the clinical study, and proper selection of the patients. In addition, CT imaging was performed to ensure dilation was not performed on patients with carotid canal dehiscence within the bony portion of the ET.

In the clinical study, technical success was high with 298/299 (99.7%) of all targeted Eustachian tubes successfully accessed and dilated under general anesthesia. There were several events considered as device malfunctions, including two devices that leaked saline upon inflation, and one device that was bent during approach into the Eustachian Tube.

Among 299 subjects who underwent Eustachian tube dilation (444 dilated ET), there were 0 serious device- or procedure-related adverse events. However, there were 16 non-serious device or procedure-related adverse events that occurred in 13 subjects. There were 2 subjects that had 3 potential device-related adverse events including mucosal tear, worsened ETD, and conductive hearing loss. The most commonly occurring non-serious device- or procedure-related adverse events were epistaxis and ETD. All potentially device- or procedure-related events were mild or moderate in severity and resolved without sequelae.

The lack of serious device- or procedure-related adverse events and the resolution of the low rate of non-serious device- or procedure-related adverse events in the study strongly supports a reasonable assurance of safety for use of the device for ET dilation for adult patients with persistent ETD.

The probable benefits of the device are based on data collected in a clinical study as described above. Persistent Eustachian Tube Dysfunction (ETD) was defined by patient-reported symptoms of ETD (including pressure and/or pain and/or clogged and/or muffled sensation in the affected ear(s)) and documented evidence that the subject has experienced persistent ETD symptoms for 12 weeks or greater. Patients must have failed appropriate medical management consisting of either a minimum of 4 weeks of continuous daily usage of any intranasal steroid spray (INS) or a minimum of one completed course of an oral steroid.

The results of the clinical study show that a greater proportion of subjects in the investigational arm demonstrated tympanogram normalization (51.8%, 73/141) compared to the control arm (13.9%, 10/72). Based on the scores from a widely used validated subjective questionnaire for evaluating and diagnosing ETD, the Eustachian Tube Dysfunction Questionnaire (ETDQ-7), a greater proportion of the subjects in the investigational arm (90.6%, 126/139) compared to the control arm (45.1%, 32/71) also reported enhancement in the quality of life at 6 weeks as measured using the minimally important difference (MID) level improvement of 0.5 points at 6 weeks post-treatment. Subjects in the investigational arm also showed a greater improvement in ETDQ-7 score at 6 weeks compared to control. Investigational subjects reported a -2.3 (1.4) mean (standard deviation) improvement in ETDQ-7 score at 6 weeks compared to -0.5 (1.2) for control subjects, and a greater proportion (56.1%, 78/139) of investigational subjects reported an ETDQ-7 mean item score of less than 2.1 at 6 weeks compared to 8.5% (6/71) for control subjects. The analysis of the overall results also showed there was no significant variation in health benefit for different demographic subpopulations; it appeared that the lead in subjects, subjects randomized to the treatment arm and those randomized to the control arm were comparable with respect to demographics and baseline characteristics.

However, the data demonstrated a degree of variation with regards to the treatment effect at the primary endpoint at 6 weeks; the possible explanations for the treatment by site interaction could include device and procedural learning curve of the investigators, subject and/or site conformance to the protocol, or statistical variance. Training on cadavers is therefore necessary to mitigate variations in treatment across multiple users and sites.

Durability of treatment effect is supported by sustained primary effectiveness outcomes for over 170 subjects, where a greater proportion of randomized treated (62.2%, 61/98) and lead-in subjects (58.1%, 43/74) demonstrated tympanogram normalization at 24 weeks post-procedure 51.8% (73/141) and 40.0% (30/75) compared to those at 6 weeks, respectively. Durability was also consistently demonstrated across secondary efficacy outcome measures where improvement in ETDQ-7 scores and proportion of subjects without symptomatic dysfunction are sustained at 24 weeks post-procedure.

Altogether, the efficacy results are supportive of greater improved outcomes for ETBC-treated patients compared to control, as well as a durable treatment effect.

Patient Perspectives

Patient perspectives considered for the ACCLARENT AERA™ Eustachian Tube Balloon Dilation System included:

The use of the improvement in the Eustachian Tube Dysfunction Questionnaire (ETDQ-7) scores, as part of the secondary efficacy endpoint evaluation. The ETDQ-7 is a validated symptom score used in assessing adult patients with Eustachian Tube Dysfunction. The results of the ETDQ-7 score are discussed above.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that for dilating the cartilaginous portion of the Eustachian tube for treating persistent Eustachian tube dysfunction, the probable benefits outweigh the probable risks for the ACCLARENT AERA™ Eustachian Tube Balloon Dilation System. The device provides substantial benefits and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The *de novo* request for the Acclarent Aera™ Eustachian Tube Balloon Dilation System is granted and the device is classified under the following:

Product Code: PNZ

Device Type: Eustachian Tube Balloon Dilation System

Class: II

Regulation: 21 CFR 874.4180