Title: Tympanoseal (Tympanic Membrane Device) Clinical Study

Number: NCT02918942

Date: 7/12/2017

Contents: Study Protocol.

TYMPANOSEAL RESEARCH PROTOCOL
GRACE MEDICAL, INC.

Protocol Number	2015.01 - Rev. B
Version Date:	07/12/2017
Investigational Product:	Tympanoseal
Sponsor:	Grace Medical, Inc. 8500 Wolf Lake Drive Suite 110 Memphis, TN 38133-4104
Principal Investigator:	Name: E-mail:

Approval:

Sponsor Signature (Name and Title) Date

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Grace Medical, Inc. with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 2015.01 – Rev. B

Protocol Title: **Tympanoseal Research Protocol**

Protocol Date: July 12, 2017

_____ _____

Investigator Signature Date

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Print Name and Title

Site # _____

Site Name _____

Address _____

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Phone Number _____

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List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
PI	Principal Investigator
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect

PROTOCOL SYNOPSIS

TITLE	**Tympanoseal Research Protocol**
SPONSOR	Grace Medical, Inc.
NUMBER OF SITES	2
RATIONALE	This investigational clinical study is to assess the safety of Tympanoseal, a sodium/calcium alginate tympanic membrane perforation device that acts as a scaffold during the healing process. It is intended for use following removal or extrusion of indwelling tympanostomy tubes or traumatic injury of the tympanic membrane.
STUDY DESIGN	This is a non-randomized, non-blinded study.
PRIMARY OBJECTIVE	The purpose of this investigational study is to assess the safety of Tympanoseal when used during the healing process.
SECONDARY OBJECTIVES	Determine if any adverse events occur during presence of material on tympanic membrane.
NUMBER OF SUBJECTS	Up to 15 at each site
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1) Male or female patients over 2 years of age at enrollment 2) Documentation of a retained tympanostomy tube or persistent perforation less than 5 mm. 3) Written informed consent (and assent when applicable) obtained from subject or subject's legal guardian and ability for subject to comply with the requirements of the study Exclusion Criteria: 1) Active otorrhea or otitis media 2) History of cholesteatoma 3) Perforations on the edge of the tympanic membrane 4) Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data 5) Subject is taking systemic/oral corticosteroids 6) Subject will require the continued use of any type of topical otic medication to the ear(s) with Tympanoseal.
RESEARCH PRODUCT	Tympanoseal will be placed during a surgical procedure.

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects may be in study for up to 36 weeks. Subjects may exit study at any follow-up visit if healing is noted by investigator. It is expected that there will be up to 3 follow-up visits after surgery: 4 weeks (± 7 days) 10 weeks (± 7 days) 16 weeks (± 14 days) However, additional follow-up visits may be scheduled (until no product remains visible) at 20 weeks (± 14 days), 24 weeks (± 14 days), 30 weeks (± 14 days), 36 weeks (± 14 days). Subjects may exit study at any interval after Tympanoseal device is no longer present. Additional visits may also be scheduled per investigator discretion. Estimated total duration of the study is expected to be 18 months from subject recruitment to final subject follow-up.
CONCOMITANT MEDICATIONS	Prohibited: Chronic systemic/oral corticosteroids Topical medications for the ear unless medically necessary
EFFICACY EVALUATIONS	Otomicroscopy with photograph of tympanic membrane at each Follow-Up Visit until Study Exit
PRIMARY ENDPOINT	Healing of Tympanic Membrane
SECONDARY ENDPOINTS	Resorption of Tympanoseal
SAFETY EVALUATIONS	Examination during follow-up visits will establish an incidence of adverse events to the implantation of Tympanoseal
PLANNED INTERIM ANALYSES	Due to short time-frame of this study, no interim analyses are planned. Serious adverse events will be monitored on an ongoing basis throughout the study.
STATISTICS	As this study is for safety and utilizing a small number of subjects, no statistical analysis will be completed. Information will be presented to the FDA in tabular format.
RATIONALE FOR NUMBER OF SUBJECTS	Suggested by the FDA during pre-510(k) conference call.

1 BACKGROUND

The purpose of this investigational study is to assess the ability of Tympanoseal (sodium/calcium alginate), an investigational device, to act as a scaffold during healing of the tympanic membrane. Tympanoseal is intended for use following removal or extrusion of indwelling tympanostomy tubes or traumatic injury of the tympanic membrane.

Formulation of Tympanoseal

Tympanoseal is formulated from a hydrogel consisting of sodium and calcium mixed salt of alginic acid.

Grace Medical, in cooperation with Cliff Megerian MD of Case Western Reserve University has developed Tympanoseal, a sodium/calcium alginate tympanic membrane scaffolding device to address the issues in existing state of the art technologies. It will be available as one device that can be trimmed to four different sizes.

Tympanoseal devices were constructed using an injection molding technique which results in gels composed of 2.7% Pronova™ calcium alginate and 1.8% Pronova™ sodium alginate (Melvik et al., United States Patent 7,790,600, September 7,2010). This gelling methodology is proprietary to NovaMatrix, AS of Drammen, NO, and is marketed as a self-gelling alginate. Upon solidification the hydrogel appears very light, opaque beige.

Figure 1. Tympanoseal plug

Different sizes as measured by the diameter of the inter-flange shaft will be available including 2mm, 3mm, 4mm and 5mm. Tympanoseal will be provided lyophilized in a special capsule made of medical-grade transparent Nylon 12 which has been proven to be both sterilizable and non-contaminating to medical devices. The device is removed by breaking tabs on the bottom section, taking off the top section and removing the contents with forceps. The product comes in a Christmas tree shape. The physician selects the correct size and removed by cutting what is not needed.

1.1 Overview of Non-Clinical Studies

Review of Grace Medical Tympanoseal Sodium/Calcium Alginate Seal Test Data

Hott ME, Megerian CA, Beane R, Bonassar LJ. Fabrication of tissue engineered tympanic membrane patches using computer-aided design and injection molding.
Laryngoscope. 2004 Jul; 114(7):1290-5.

Chronic tympanic membrane perforation patches were fabricated by molding alginate loaded with bovine articular chondrocytes into a bobbin-shaped construct. Chondrocytes were cultured for 10 weeks and assessed for mechanical and dimensional stability. Extracellular matrix was continually deposited and was rich in collagen and proteoglycans.

Weber DE, Semaan MT, Wasman JK, Beane R, Bonassar LJ, Megerian CA. Tissue-engineered calcium alginate patches in the repair of chronic chinchilla tympanic membrane perforations.
Laryngoscope. 2006 May;116(5):700-4.

The publication describes the comparison of alginate hydrogel grafts versus application of a paper patch in a chinchilla model of tympanic membrane perforation. The alginate treated perforations demonstrated significantly improved healing rates over both the untreated control group and the paper patch control group. Nine of thirteen healed in the alginate group, two of nine in the paper patch group and one of eleven in the control group. It was concluded that calcium alginate tympanic grafts offer significant advantages in the treatment of chronic tympanic membrane perforations over traditional methods.

Biocompatibility Test Data

Tympanoseal (sodium/calcium alginate scaffold) is deemed to be biocompatible and presents no infection risk in humans. Results of testing are summarized below. Biocompatibility tests were performed with NovaMatrix sodium and calcium alginates used to fabricate Tympanoseal.

Test Material	Biocompatibility Test	Test Source	Results
LVG Pronova™ Sodium Alginate	Cytotoxicity based on *in vitro* cell culture of 3T3 mouse fibroblasts and V79 Chinese hamster	NovaMatrix Drug Master File 14993	No effects on cell survival or ability to form colonies.
LVG Pronova™ Sodium Alginate (132 mPas viscosity)	Acute systemic toxicity by intraperitoneal route mouse	NovaMatrix Drug Master File 14993	No mortaility or abnormal clinical signs with normal weight gain
LVG Pronova™ Sodium Alginate (132 mPas viscosity)	Acute systemic toxicity by intraperitoneal route rat	NovaMatrix Drug Master File 14993	No mortaility or abnormal clinical signs with normal weight gain
LVG Pronova™ Sodium Alginate (30 mPas viscosity)	Acute systemic toxicity by intraperitoneal route rat	NovaMatrix Drug Master File 14993	No mortaility or abnormal clinical signs with normal weight gain
LVG Pronova™ Sodium Alginate 3.5 mPas viscosity)	Acute systemic toxicity by intraperitoneal route rat	NovaMatrix Drug Master File 14993	No mortaility or abnormal clinical signs with normal weight gain
LVG Pronova™ Sodium Alginate	Hemolysis	NovaMatrix Drug Master File 14993	No lysis of blood cells recorded
LVG Pronova™ Sodium Alginate	Implantation in rabbits	NovaMatrix Drug Master File 14993	Moderate inflammatory responses with no implant material remaining at site of implantation. Slightly greater tissue reaction was observed than at the sham operation site.
LVG Pronova™ Calcium Alginate	Cytotoxicity based on *in vitro* cell culture of 3T3 mouse fibroblasts	NovaMatrix Drug Master File 20497	Material had no cytotoxic effects on either cell lines

	and V79 Chinese hamster		
LVG Pronova™ Calcium Alginate	Acute systemic toxicity rats, s.c.	NovaMatrix Drug Master File 20497	No evidence of toxicity
LVG Pronova™ Calcium Alginate	Acute systemic toxicity rats, i.m.	NovaMatrix Drug Master File 20497	No evidence of toxicity
LVG Pronova™ Calcium Alginate	Subchronic toxicity Sprague Dawley rats, Charles River Laboratory	NovaMatrix Drug Master File 20497	No signs of toxic effects and no weight loss over study period
LVG Pronova™ Calcium Alginate	LD50 i.p. in rats	NovaMatrix Drug Master File 20497	1,407 mg/kg lethal dose in rats
LVG Pronova™ Calcium Alginate	LD50 i.v. in rats	NovaMatrix Drug Master File 20497	64 mg/kg lethal dose in rats
LVG Pronova™ Calcium Alginate	Rat implantation, dorsal left scapula of calcium alginate slurry in normal saline	NovaMatrix Drug Master File 20497	No signs of systemic toxicity, granulomas in two animals, foreign body reaction shortly after implantation
NovaMatrix self gelling sodium/calcium alginate gel	Rat implantation, dorsal right scapula and hindlimb of self gelling sodium/calcium alginate in normal saline	NovaMatrix Drug Master File 20497	No adverse systemic signs, no weight change and gelatinous thickening at the injection site days 3, 15, 31 and 60.
NovaMatrix self gelling sodium/calcium alginate gel	Rat subcutaneous injection	NovaMatrix Drug Master File 20497	No adverse toxic effects recorded, day 3 revealed cell infiltration, days 15 and 60 foreign body reaction
NovaMatrix self gelling sodium/calcium alginate gel	Rat intramuscular injection	NovaMatrix Drug Master File 20497	No adverse toxic effects recorded, day 3 revealed cell infiltration, days 15 and 60 foreign body reaction
NovaMatrix self gelling sodium/calcium alginate gel, as manufactured for Grace Medical	ISO MEM elution using L-929 mouse fibroblast cells	WuXi Apptec report to Grace Medical, Inc.	Test article is not considered cytotoxic according to the conditions of this test.
NovaMatrix self gelling sodium/calcium alginate gel, as manufactured for Grace Medical	ISO intracutaneous irritation test	WuXi Apptec report to Grace Medical, Inc.	Score of 1 according to ISO protocols, was not irritating

NovaMatrix self gelling sodium/calcium alginate gel, as manufactured for Grace Medical	ISO Guinea pig maximization sensitization test, 2 extracts	WuXi Apptec report to Grace Medical, Inc.	Under the conditions of this protocol the test article did not elicit a sensitization response.
NovaMatrix self gelling sodium/calcium alginate gel, as manufactured for Grace Medical	ISO In vivo mouse micronucleus assay	WuXi Apptec report to Grace Medical, Inc.	The test article is considered non-mutagenic in this test system.
NovaMatrix self gelling sodium/calcium alginate	ISO mouse lymphoma with extended treatment	WuXi Apptec report to Grace Medical, Inc.	Test article was found to be non-mutagenic (non-genotoxic and non-clastogenic)
NovaMatrix self gelling sodium/calcium alginate	ASTM Hemolysis Assay-Direct Contact and Extraction Method	WuXi Apptec report to Grace Medical, Inc.	Test material was not hemolytic
NovaMatrix self gelling sodium/calcium alginate	Complement Activation C3a and SC5b-9	WuXi Apptec report to Grace Medical, Inc.	Test article did not activate complement more than control
NovaMatrix self gelling sodium/calcium alginate	ISO In Vivo Mouse Micronucleus Assay	WuXi Apptec report to Grace Medical, Inc.	Test article was not genotoxic
NovaMatrix self gelling sodium/calcium alginate	ISO Bacterial Mutagenicity Test-Ames Assay	WuXi Apptec report to Grace Medical, Inc.	Test article was not mutagenic

Ototoxicity testing of calcium alginate samples using Grace Medical's proprietary method was performed by Dr. Hinrich Staecker and Jennifer Nelson Brantley of the University of Kansas Medical Center. The Auditory & Vestibular Neuroscience Lab tested the ototoxicity by using an in- mouse model when exposed to Grace Medical's alginate formulation via surgical implantation.

Conclusions: "There was no evidence of any hearing loss either in the acute or late period after alginate placement. No evidence of balance problems were seen on behavioral evaluation. Evaluation of animals after termination of experiment demonstrated that all the material had absorbed."

1.2 Overview of Clinical Studies

Adverse Events Associated with NovaMatrix Self Gelling Alginate

Clinical trials of Algisyl (Lone Star Heart, Laguna Hills, CA) a cardiac repair gel made with NovaMatrix self gelling alginate have demonstrated adverse events in 21.4% of test subjects. None of these events have been related to alginate itself but to development of infections or worsening of heart conditions No other occurrences of adverse events from use of NovaMatrix self gelling alginate have been found.

2 STUDY RATIONALE

This study will provide data on the safety and the ability of sodium/calcium alginate gels to act as a scaffold capable of occluding a tympanic membrane perforation over the duration of complete healing. Tympanoseal could be used in cases where cartilage or fat graft tympanoplasty would be indicated.

2.1 Risk / Benefit Assessment

Risk Versus Benefits to the Subjects

Risk levels are assessed on the severity level and the likelihood of occurrence. Both severity and occurrence levels for the risks assessed were considered low in this study.

Risk	Risk Level	Mitigation
Bio-incompatible – adverse reaction to the tympanic membrane	Low	Biocompatibility tests
Insufficient coverage of the TM perforation	Low	Range of Calcium alginate seal size available up to 5 mm
TM perforation does not fully repair / enlarges	Low	Results of Chinchilla study
Sclerosis of the TM	Low	Results of Chinchilla study
Granulation tissue remains resulting in delayed healing	Low	Results of Chinchilla study
Hemorrhage of TM	Low	Results of Chinchilla study
Hearing loss either poor or worsens	Low	Results of Chinchilla study
Lateral Displacement of Material	Low	Operative Technique indicates that larger flange is placed laterally.

The anticipated benefits of Tympanoseal are as follows:

1. Potential improvement in perforation repair rate indicated by chinchilla study.

2. Calcium alginate has been proven to increase fibroblast proliferation needed to produce collagen in the creation of a stable lamina propria layer. No current perforation seal repair material enables regeneration of the natural lamina propria.

3. Ease of application which will be similar to vent tube placement.

4. Calcium ions in the seal will exchange for sodium ions in exudates of the tympanic membrane wound potentially enhancing hemostasis and allowing collagen deposition to establish a stable lamina propria.

5. No risk of lateralization found in underlay techniques of tympanoplasty which may result in hearing loss and cholesteatoma.
   (Jung TT, Park SK. Mediolateral graft tympanoplasty for anterior or subtotal tympanic membrane perforation. Otolaryngol Head Neck Surg . 2005 Apr;132(4):532-6).

6. No need for Gelfoam to be placed under the seal to support it and eliminates the risk of fibrosis in the middle ear reported with Gelfoam.
   (Smith J, Gardner E, Dornhoffer JL.Hearing results with a hydroxylapatite/titanium bell partial ossicular replacement prosthesis. Laryngoscope. 2002 Oct;112(10):1796-9.)

7. Supplying surgeons with an FDA approved device to act as scaffolding for tympanic membrane perforation repair. Currently all other products act as simple films and do not occlude a perforation.

The potential benefits described outweigh the low level of risk.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to assess the safety of Tympanoseal when used as scaffolding during the healing process.

3.2 Secondary Objectives

The secondary objective is to determine ability / if any adverse events arise from implantation of Tympanoseal such as colonization by microorganisms or diminution of hearing by damping of tympanic membrane vibrations.

4 STUDY DESIGN

This study will be a non-blinded, non-randomized trial. There will be two (2) sites with a limit of fifteen (15) subjects at each site. (Up to thirty (30) total subjects are planned.) Each subject will have Tympanoseal placed during a surgical procedure.

Evaluations will be taken at baseline and up to three evaluations at 4, 10 and 16 weeks. If tympanic healing is noted at any visit, then the subject may exit the study without need for additional follow-up evaluations.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. All subjects will be treated with surgically implanted Tympanoseal, either unilaterally or bilaterally as needed.

Total duration of subject participation will be up to 16 weeks post-procedure and total study duration is estimated to be 6 months.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary endpoint will be the healing of the tympanic membrane perforation. In chinchillas this occurred between 1 and 2 months.

5.2 Secondary Efficacy Endpoints

Secondary study endpoint at 16 weeks will establish that the Tympanoseal has fully resorbed and is no longer visible.

5.3 Safety Evaluations

Examination during follow-up visits will establish an incidence of adverse events to the implantation of Tympanoseal.

6 SUBJECT SELECTION

6.1 Study Population

Subjects with retained tympanostomy tube(s) or persistent central tympanic perforation of less than 5mm will be enrolled in this study.

6.2 Inclusion Criteria

1. Male or female patients over 2 years of age at enrollment.
2. Documentation of a retained tympanostomy tube or persistent perforation less than 5 mm.
3. Written informed consent (and assent when applicable) obtained from subject or subject's legal guardian and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

1. Active otorrhea or otitis media
2. History of cholesteatoma
3. Perforations on the edge of the tympanic membrane.
4. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
5. Subject is taking systemic/oral corticosteroids
6. Subject will require the continued use of any type of topical otic medication to the ear with Tympanoseal

7 Concomitant Medications

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapies are allowed except for treatments noted in the exclusion criteria described above and as noted in the prohibited medications section below.

7.2 Prohibited Medications and Treatments

The following medications are prohibited during the study and administration will be considered a protocol violation:

1. Systemic/oral corticosteroids
2. Use of any topical medication to the ear immediately following surgery.

Articles that justify the prevention of the use of systemic corticosteroids are provided below.

Kaftan H. Hosemann W. Topical Application of Mitomycin C in Combination with Dexamethasone: Effective Delay of Myringotomy closure.
ORL J Otorhinolaryngol Relat Spec. 2006;68(4):185-8.

Kaftan H, Hosemann W. Systemic Corticoid Application in Combination with Topical Mitomycin or Dexamethosone: Inhibition of Wound Healing after Tympanic Membrane Perforation.
HNO. 2005 Sep;53(9):700-83.

8 STUDY TREATMENT

All subjects will receive the investigational device, Tympanoseal.

8.1 Blinding / Randomization

This is a non-blinded, non-randomized study.

8.2 Formulation of Tympanoseal

Tympanoseal is formulated from a hydrogel consisting of sodium and calcium mixed salt of alginic acid. The sodium/calcium alginate devices were constructed using an injection molding technique which results in gels composed of 2.7% Pronova™ calcium alginate and 1.8% Pronova™ sodium alginate (Melvik et al., United States Patent 7,790,600, September 7,2010). This gelling methodology is proprietary to NovaMatrix, AS of Drammen, NO, and is marketed as a self-gelling alginate. Additional information was provided in Section 1.

8.3 Packaging and Labeling

Packaging:
Tympanoseal is provided sterile in a protective, transparent nylon capsule inside a transparent moisture barrier pouch.

Labeling:
Each package of study device will be labeled with the required FDA warning statement, the catalog and lot numbers, the name of the sponsor, and directions for patient use and storage. Instructions for Use will also be included.

8.4 Device Usage

One device will be used per treated tympanic membrane.

8.5 Dispensing

The approved investigator at the site will store the device and control the use of the test article.

8.6 Instructions for Use

Operative Technique

This technique description is the suggested treatment for the uncomplicated procedure. The preferred treatment is that which addresses the needs of the specific patient. The perforation site is evaluated under the operating microscope and the edges of the perforation are manipulated with a small pick so as to freshen the margins of the perforation.

A perforation sizing device will be provided with each device which will allow the surgeon to estimate the diameter of a hole in the tympanic membrane in order to choose a repair construct of appropriate size.

The lyophilized device is provided in a protective capsule with four sizes each attached to the other with progressively smaller flanges along its length. The capsule is opened by bending the lateral tabs on its larger bottom portion with one hand while carefully removing the smaller top portion with the other hand. The device can be easily extracted with forceps.

The proper size for a given perforation is excised with surgical scissors or scalpel. One flange will be of a larger diameter than the other; the surgeon will implant the device with the larger flange laterally. Insertion of Tympanoseal is similar to the placement of a tympanostomy tube. Immediately after insertion normal saline should be instilled in the external auditory canal to swell the device and completely occlude the perforation.

After Tympanoseal is in place, wax earplugs should be in place during showers and swimming.

8.7 Supply of Study Device at the Site

The Sponsor will ship Study Device to the investigational sites. The initial study device shipment will be made after site activation (i.e., all required regulatory documentation has been received by the Sponsor and a contract has been executed). Subsequent study device shipments will be made at site request for resupply.

8.8 Study Device Accountability

Study devices should be stored by the study site at room temperature.

An accurate and current accounting of the dispensing of study devices will be maintained on an ongoing basis by a member of the study site staff. The number of study devices received and used will be recorded on the Investigational Device Accountability Record. The study monitor will verify these documents throughout the course of the study.

8.9 Measures of Treatment and Compliance

Subjects are required to return for follow-up visits. Each will be instructed to contact investigator's office for questions or need for unscheduled visit.

9 STUDY PROCEDURES AND GUIDELINES

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject or subject's legal guardian If appropriate, assent must also be obtained prior to conducting any study-related activities.

The preoperative visit will include a medical history, physical examination, prior ENT history, concomitant medications and otomicroscopy with photograph of the tympanic membrane perforation prior to use of Tympanoseal. A photograph will also be taken after product has been inserted.

Subjects enrolled in the study will be required to return for up to three follow-up evaluations after surgery at 4 weeks, 10 weeks and 16 weeks. If tympanic healing is noted at any visit, then the subject may exit the study without need for additional follow-up evaluations.

It is expected that the product will have resorbed (dissolved) prior to 16 weeks. However, if Tympanoseal is visible at the 16 week visit, the subject should have additional follow-up visits scheduled until no product remains at 20 weeks (± 14 days), 24 weeks (± 14 days), and 36 weeks (± 14 days). Subjects may exit study at **any interval** when Tympanoseal is no longer present. Additional visits may be scheduled per investigator discretion.

If the Tympanoseal product appears 'dry' to the Investigator, 3-5 drops of saline may be added to keep it moist. (This should be noted in the comments section of the CRF.)

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medications and concurrent therapies will be documented at enrollment, day of procedure, post-operative follow-up visits, and study exit. Dose, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at enrollment.

9.1.3 Medical History

Relevant medical history, including prior ENT history, cause and size of perforation and length of time present, allergies, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Enrollment.

9.1.4 Physical Examination

A physical examination will be performed by either the investigator or a sub-investigator who is a physician at enrollment. Qualified staff (MD, NP, RN, and PA) may complete an abbreviated physical exam at all other visits. New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

9.1.5 Vital Signs

Body temperature, pulse and respirations will be recorded at each visit. Height and weight will also be obtained.

9.1.6 Otomicroscopy with Photograph of Tympanic Membrane

At each visit otomicroscopy with photograph of tympanic membrane is required.

9.1.7 Adverse Events

Information regarding occurrence of adverse events will be captured from procedure date to study completion. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study device will be recorded on the Adverse Event Tracking Log.

10 EVALUATIONS BY VISIT

Please note that it is acceptable for the Enrollment and Procedure to occur on the same day. Duplicate tasks do not need to be performed and duplicate CRFs are not required to be completed. See section 10.3 for additional information.

10.1 Enrollment / Pre-operative Visit

1. Review the study with the subject (subject's legal guardian) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Assign the subject a unique screening number.
3. Record demographics data.

4. Record general medical history and prior ENT history including the cause and size of perforation and length of time present, allergies, and other pertinent respiratory history.
5. Record concomitant medications.**
6. Perform physical examination, including vital signs.**
7. Otomicroscopy with photograph of tympanic membrane prior to procedure.**
8. Schedule subject for surgical procedure.

10.2 Day of Procedure

1. Concomitant medications review.***
2. Perform abbreviated physical examination.***
3. Perform and record vital signs.***
4. Completion of Procedure and Device Information CRF.
5. Otomicroscopy with photograph of tympanic membrane after procedure with Tympanoseal in place.**
6. If applicable, record any Adverse Events.

**Note: See information below if enrollment and procedure are on the same day.

10.3 If Enrollment and Procedure are on the same day, the following tasks and CRFs are required to be completed.

1. Review the study with the subject (subject's legal guardian) and obtain written informed consent and HIPAA authorization and assent, if appropriate.
2. Assign the subject a unique screening number.
3. Record demographic data. (Enrollment / Demographics CRF)
4. Complete Eligibility Criteria CRF
5. Record general medical history and prior ENT history including the cause and size of perforation and length of time present, allergies, and other pertinent respiratory history. (Medical History (General) and ENT History CRF's)
6. Record concomitant medications. (Concomitant Medication CRF)
7. Perform physical examination, including vital signs. (Pre-Procedure Visit CRF)
8. Otomicroscopy with photograph of tympanic membrane **prior** to procedure.
9. Completion of Procedure and Device Information CRF.
10. Otomicroscopy with photograph of tympanic membrane **after** procedure with Tympanoseal in place.
12. If applicable, record any Adverse Events.

10.4 Follow-up Evaluation - 4 weeks (± 7 days)

1. If applicable, record any new Adverse Events.
2. Record changes to concomitant medications.

3. Perform abbreviated physical examination.
4. Perform and record vital signs.
5. Otomicroscopy with photograph of tympanic membrane

   Note: If complete healing is noted, then patient may exit the study and Subject Study CRF should be completed.

10.5 Follow-up Evaluation - 10 weeks (± 7 days)

1. If applicable, record any new Adverse Events.
2. Record changes to concomitant medications.
3. Perform abbreviated physical examination.
4. Perform and record vital signs.
5. Otomicroscopy with photograph of tympanic membrane

   Note: If complete healing is noted, then patient may exit the study and Subject Study CRF should be completed.

10.6 Follow-up Evaluation - 16 weeks (± 14 days) (and additional visits as applicable. See 10.7).

1. If applicable, record any new Adverse Events.
2. Record changes to concomitant medications.
3. Perform abbreviated physical examination.
4. Perform and record vital signs.
5. Otomicroscopy with photograph of tympanic membrane

Note: If complete healing is noted, then patient may exit the study and Subject Study CRF should be completed.

10.7 Potential Additional Follow-Ups at 20 weeks (± 14 days), 24 (± 14 days), 30 (± 14 days), 36 weeks (± 14 days) as needed.

It is expected that the Tympanoseal will have resorbed prior to 16 weeks. However, additional visits should be scheduled for 20 weeks, 24 weeks, 30 weeks and 36 weeks until no product remains. The subject may exit the study at any of these intervals after the device is no longer present.

1. If applicable, record any new Adverse Events.
2. Record changes to concomitant medications.
3. Perform abbreviated physical examination.
4. Perform and record vital signs.
5. Otomicroscopy with photograph of tympanic membrane

Note: If complete healing is noted, then patient may exit the study and Subject Study CRF should be completed.

Unscheduled Visit CRF pages will be used to capture 20, 24 and 30 week follow-ups, if needed.

10.8 Unscheduled Visit(s)

1. If applicable, record any new Adverse Events.
2. Record changes to concomitant medications.
3. Perform complete physical examination, record vital signs, and study evaluations.
4. Otomicroscopy with photograph of tympanic membrane
5. Please note the reason for the visit in the comments section.

   Note: If complete healing is noted at this visit, the patient may exit the study and Subject Study CRF should be form completed.

11 ADVERSE EVENT REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a medical device and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product.

The Investigator will determine with the subject, the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study device, or if unrelated, the cause.

AE Severity Grading

The guidelines below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious. (A 'severe' headache may not be a 'severe' AE.)

The collection period for all AEs will begin after device is implanted and ends at Subject Exit.

AE Severity Grading

Severity	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required,, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Device

The relationship of an AE to the study device should be assessed using the following the guidelines.

Relationship to Device	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from use of the device; that follows a known or expected response pattern
Probably	An event that follows a reasonable temporal sequence from use of device; that follows a known or expected response pattern and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from use of the device; that follows a known or expected response; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study device.

11.2 Serious Adverse Event (SAE)

An SAE is defined as any AE occurring that results in any of the following outcomes:

1. Death
2. A life-threatening adverse experience
3. An inpatient hospitalization or prolongation of existing hospitalization
4. A persistent or significant disability/incapacity
5. A congenital anomaly/birth defect
6. Required Intervention to Prevent Permanent Impairment or Damage

Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.3 Serious Adverse Event Reporting

Study sites will document all SAEs that occur (whether or not related to study device). The collection period for all SAEs will begin after device is implanted and ends at Subject Exit.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB), the site investigator will report SAEs to the IRB within timeframe required. Please notify Grace Medical within 5 working days.

11.4 Unanticipated Adverse Device Effects

If an SAE is also an unanticipated adverse device effect, the investigator must submit to Grace Medical (within 3 business days) and reviewing IRB a report but within 10 working days.

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a partial list of possible reasons for study treatment discontinuation:

1. Subject withdrawal of consent (or assent)
2. Lost to or refused follow-up
3. Adverse Event or Serious Adverse Event if investigator feels that it is in the best interest of the patient.

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all applicable remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the sponsor feels that it is not in the subject's best interest to continue.

The reason for the subject's withdrawal from the study will be specified in the subject's source documents as well as Study Exit Form

12.3 Replacement of Subjects

Subjects who withdraw from the study may be replaced up to a total of 15 for the site.

13 PROTOCOL DEVIATIONS

A protocol deviation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol deviations for this study include, but are not limited to, the following:

1. Failure to Obtain Informed Consent
2. Failure to meet inclusion/exclusion criteria (Eligibility)
3. Failure to maintain study evaluation time frames for follow-up visits

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol deviation. The Sponsor will determine if a protocol deviation will result in withdrawal of a subject.

When a protocol deviation occurs, it will be discussed with the investigator and a Protocol Deviation Form detailing the deviation will be completed. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

Protocol deviations should also be reported as required to the site's IRB.

14 STATISTICAL METHODS AND CONSIDERATIONS

As this study is for safety and utilizing a small number of subjects, no statistical analysis will be completed. Information will be presented to the FDA in tabular format.

Adverse event rates will be coded by body system will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study device.

14.1 Sample Size and Randomization

Up to 30 subjects will be enrolled in this non-randomized study. The number of subjects was determined by discussion with the FDA.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study device.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the Case Report Forms (CRFs) provided when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by subject number and initials.

If any correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. Copies of the completed CRFs will remain at the Investigator's site at the completion of the study.

15.2 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the study has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

15.3 Monitoring

Grace Medical, Inc. will serve as the sponsor of this investigational clinical study. It is the responsibility of the sponsor of this clinical study to ensure proper monitoring to see that the study is conducted in full compliance with the study protocol in conformance to Title 21, Code of Federal Regulations (CFR) Parts, 50, 54, 56, and 812, Guidelines for the Monitoring of Clinical Investigations and the Declaration of Helsinki, as amended. The study will be monitored by a Clinical Research Associate or designee of Grace Medical (Clinical Monitor).

By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.3.1 SITE INITIATION VISIT

Once all regulatory documents and approval are received, a site initiation visit will be scheduled. During this visit, the Monitor will review the following with the Principal Investigator and his/her staff as appropriate:

1. Study goals and obligations
2. Protocol procedures (with particular attention to inclusion/exclusion criteria, enrollment goals, adverse events, primary efficacy variables and GCP compliance)
3. Informed consent procedure
4. AE/SAE reporting
5. CRF completion and error correction/need for adequate source documentation
6. Maintenance of the investigator binder and site visit log
7. Investigational status of test article and requirements for accountability
8. Any other issue as deemed important to the conduct of the study

At this time, the following documents will be obtained if not already forwarded to Grace Medical:

1. Copy of IRB/EC approval letter
2. Copy of IRB/EC approved informed consent document
3. Signed Clinical Trial Research Agreement
4. Curricula vitae and Medical Licenses for the Principal Investigator and each Sub-Investigator
5. Financial Disclosure Form

15.3.2 INTERIM MONITORING VISITS

The first interim monitoring visit at each site will be made after the majority of subjects have completed the four week follow-up visit unless it is determined that a visit should be made earlier. The Clinical Research Associate or designee will maintain personal contact with the Investigator(s) and study personnel by telephone, mail, email and on-site visits. The Clinical Research Associate or designee will require access to all subject and study records in order to verify that:

1. Informed consent has been obtained for each subject
2. The site is in compliance with the study protocol
3. Source documentation and CRF completion
4. Study administration records are complete
5. Product inventory is verified and accurate

The Study Site Documentation Binder will also be reviewed. Additional monitoring visits will be scheduled as appropriate.

15.3.3 FINAL MONITORING VISIT

At the close of the study, the Clinical Research Associates or designee will conduct a final visit to conduct the following:

1. Collect outstanding data
2. Insure the completeness of study files
3. Review record retention requirements with study personnel
4. Provide for disposition of any remaining study supplies and devices.

15.3.4 STUDY SITE DOCUMENTATION BINDER

The Study Coordinator at each site will be trained on the proper maintenance of the Study Site Documentation Binder (Regulatory Binder). Correspondence, agreements, and logs are to be kept up–to date and copies should be forwarded to the Sponsor in a timely fashion.

The contents of the Study Site Documentation Binder may include but are not limited to:

1. Clinical Trial Research Agreement / contract
2. Financial Disclosure Forms
3. IRB Approval & Correspondence
4. IRB Approved Consent Form
5. Investigator CVs (signed & dated)
6. Training / Meeting Log
7. Signature Log
8. Device Log
9. Screening Log
10. Patient Enrollment Log
11. Sponsor Monitoring Log
12. Study Communication

15.4 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards

The protocol and consent form will be reviewed and approved by the IRB of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB's unconditional approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB. The written consent document will embody the elements of informed consent as described in the CFR 50.25. The Investigator will send an IRB -approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal guardian) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal guardian may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal guardian of the subject and the original will be maintained with the subject's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.

2. Personally conduct or supervise the study (or investigation).

3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.

4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 812

5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

6. Maintain adequate and accurate records in accordance with §21 CFR 812 and to make those records available for inspection with the Sponsor (or designee).

7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.

8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects.

9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.

10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR 812.

APPENDIX 1 SCHEDULE OF STUDY VISITS

	Enrollment*	Procedure*	Same Day Enrollment & Procedure	4 Weeks (± 7 days)	10 Weeks (± 7 days)	16 Weeks (± 14 days)	Add'l Visit(s) 20 weeks, 24 weeks, 30 weeks 36 weeks (± 14 days)
Informed Consent	X		X				
Inclusion / Exclusion	X		X				
Medical /ENT History	X		X				
Physical Exam	X*	X*	X	X	X	X	X
Vital Signs	X*	X*	X	X	X	X	X
Study Visit Evaluation	X*	X*	X	X***	X***	X***	X***
Otomicroscopy with Photograph	X**	X**	PRE & POST	X	X	X	X
Use of Study Device		X	X				
Concomitant Medication	X*	X*	X	X	X	X	X
Adverse Event****		X	X	X	X	X	X
Subject Study Exit				X***	X***	X***	X***

*Enrollment and Procedure may be the same visit and duplicate CRFs do not need to be completed. Informed Consent must be signed prior to any study procedures.

** Otomicroscopy with Photograph is required Pre and Post Procedure.

*** If healing is noted by investigator, the subject may exit the study.

**** If applicable