EVALUATION OF THE EFFICACY AND SAFETY OF AN IRREVERSIBLE ELECTROPORATION (IRE) SYSTEM FOR TONSIL REDUCTION FOR THE TREATMENT OF CHRONIC SYMPTOMATIC TONSILLAR HYPERTROPHY

Revision: **001**

Revision Date: **March 16, 2023**

Investigational Product: **IRE SYSTEM – composed of:**
IRE GENERATOR (Model No. ENTIRE001)
TONSIL HANDPIECE (Model No. ENTTON01)

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Confidentiality Statement

Document Approval Control

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Revision History

Rev.	By	Date	Description
001	Ronen Shavit	03/2023	Release
002			
003			

Protocol Signature Page

The signature below constitutes the approval of this protocol, entitled:

"Evaluation of the Efficacy and Safety of an Irreversible Electroporation (IRE) System for Tonsil Reduction for The Treatment of Chronic Symptomatic Tonsillar Hypertrophy."

and provides the necessary assurances that this trial will be conducted in compliance with all stipulations of the protocol, including all statements regarding confidentiality statements local legal and regulatory requirements, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP).

_____

Investigator's Printed Name

_____ _____

Signature ***Date***

Study Synopsis

Protocol #	CLN 0137
Study Title	Evaluation of the Efficacy and Safety of an Irreversible Electroporation (IRE) System for Tonsil Reduction for The Treatment of Chronic Symptomatic Tonsillar Hypertrophy
Study Device	IRE System composed of a generator and a handpiece (by ENTire Medical Ltd.)
Device Description	The bi-polar IRE System locally applies short, high-voltage (HV) pulses, increasing the permeability of tissue cells, creating non-thermal irreversible electroporation (NTIRE). The energy is transferred via bipolar forceps handpiece causing irreversible cell membrane perforation and apoptosis resulting in tissue reduction.
Study Design and Duration	Multi-center prospective, single arm, non-blinded study. This is a multi-center study where up to 40 patients meeting the inclusion criteria will be recruited. A minimum of 22 patients will be recruited for the implementation of statistical analysis. Pretreatment visit ('Baseline'). All subjects will undergo one treatment and will be assessed at discharge. Follow-up: 1 week (*), 1 month, and 3 months. Study duration: up to18 months from enrollment of the first patient. (*) For the first 7 days, patients will be called daily to rate their level of pain.
Investigational Treatment	Enlarged tonsil(s) mass will be reduced by ENTire IRE System. The clinical effect is anticipated within 2 to 4 weeks post-treatment.
Primary Endpoints	• Reduction of tonsil(s) size in accordance with the Brodsky Grading System for Tonsils (BGST) by at least one grade at 3 months compared to the Baseline.

	• Pain VAS at 1 week follow up visit to be non-inferior to literature[1].
Secondary Endpoints	• Snore VAS reduction at 3 months compared to the Baseline. • To evaluate procedure-related safety.
Inclusion Criteria:	• Age 18 – 70 years. • Tonsillar Hypertrophy of grade 2 or higher on the BGST.
Main Exclusion Criteria:	• Age below 18 years. • Patients with a pacemaker or similar electro stimulator. • Patients for whom the anesthesia involves high risk. • Epilepsy or other condition involving convulsions. • Inability to give informed consent and to complete self-reported questionnaires. • Patients with an inability to cooperate for treatment and follow-up. • Severe heart disease. • Pregnancy or breastfeeding. • Significant systemic illness (e.g., cancer, severe autoimmune disease, neurological disease). • Bleeding diathesis. • Patients suffering from obesity as indicated by a body mass index (BMI) > 32kg/m2. • Known or suspected complications for any general or local anesthetic agents and/or any antibiotic medications.
Effectiveness Evaluation	Effectiveness analysis will be composed of the assessment in reduction of tonsillar hypertrophy by at least one grade and a reduction in post procedure related pain as compared to literature for other surgical treatment for tonsillar reduction. Other elements that may demonstrate effectiveness include a reduction snoring. Tonsillar reduction - assessed using BGST. Pain - assessed using Pain VAS scale. Snoring - assessed using Snore VAS scale.

[1]Natural course of tonsillectomy pain: A prospective patient cohort study Kim, Min-Su et al. Auris Nasus Larynx, Volume 45, Issue 3, 508 - 513

Safety Evaluation	Safety evaluation will be based on the number of reported complications and adverse events (e.g., bleeding, numbness, infection, etc.) • Physician assessment of the incidence of post-treatment reactions will be done using a 0 to 3 grading scale (0=none, 1=mild, 2=moderate, 3=severe) following treatment and recorded any additional side effects. Further categorized as serious and non-serious, device-related, non-device-related. Adverse events will be evaluated during the procedure, at all subsequent visits, and at any unscheduled visits.

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1 INTRODUCTION

1.1 Background

1.1.1 Tonsillar Hypertrophy

Chronic Tonsillar Hypertrophy is a condition characterized by an enlarged state of the tonsil(s). The underlying causes of this condition are diverse and can include infections and allergies. In some cases, a genetic predisposition or underlying medical conditions, such as autoimmune or endocrine disorders, can contribute to the development of chronic tonsillar hypertrophy.

1.1.1.1 *Recurrent Tonsillitis and Tonsillar Hypertrophy in Adults*

Recurrent tonsillitis and chronic tonsillitis, or inflammation of the tonsil(s), is predominantly the result of a viral or bacterial infection and may present as a sore throat. For most patients, evaluation for tonsillitis includes physical examination, risk stratification by scoring systems, and consideration of rapid antigen testing and/or throat culture.

Given the frequency of viral etiologies, the mainstay of treatment of acute tonsillitis is supportive care, including analgesia and hydration; patients rarely require hospitalization. In some cases, medications can provide symptomatic relief or surgical treatments (including tonsillectomy or tonsillotomy) may be recommended.

Recurrent/chronic tonsillitis is a common indication for tonsil surgery in adults.

1.1.1.2 *SDB Tonsillar Hypertrophy*

Few studies have characterized the association of tonsillar hypertrophy in adults with Sleep Disordered Breathing (SDB) as enlarged tonsil(s) can obstruct the airway during sleep. The term SDB encompasses a spectrum of abnormalities, including snoring, Upper Airway Resistance Syndrome (UARS), Obstructive Sleep Apnea (OSA), Central Sleep Apnea (CSA), respiratory-related arousals and hypoventilation.

Enlarged tonsil(s) may lead to recurrent episodes of partial or complete airway obstruction during sleep and cause SDB. This may result in symptoms such as excessive daytime sleepiness, loud snoring, restless sleep, and frequent awakenings during the night. If left untreated, SDB can lead to serious health complications, including cardiovascular disease, diabetes, and even stroke. Thus, tonsillar reduction is often performed in patients with clinical evidence of tonsillar hypertrophy to address the cause of SDB and/or OSA.

1.1.2 Evaluation and Intervention for Chronic Tonsillar Hypertrophy

A comprehensive evaluation is necessary to diagnose and properly treat chronic tonsillar hypertrophy. During the physical examination, the healthcare provider will assess the size and appearance of the tonsil(s), as well as any other symptoms that may be present such as difficulty breathing or swallowing, sleep disturbances, or a persistent sore throat. Tonsillar enlargement may be documented using grading classification systems: Brodsky Grading System for Tonsils, Friedman Grading Scale, Modified 3-Grade Scale or Modified 5 Grade Scale. These scales allow for the categorization of tonsillar size by grading the percentage and/or the area of the

oropharyngeal airway obstructed due to one or both enlarged tonsils. Surgical intervention occurs once hypertrophy of the tonsil(s) has an impact on patients' health including, but not limited to, difficulty swallowing, recurrent/chronic infection and SDB.

1.1.2.1 ***Surgical Techniques for Tonsillar Reduction***

The tonsil reduction surgical techniques may be divided into[1]:

- Removal of the entire tonsil – tonsillectomy.
- Partial reduction of the tonsil – including tonsillotomy and tonsillar reduction.

Common techniques are presented herein[2]:

Electrocautery

Electrocautery is a surgical technique that uses electrical current to produce heat to remove tissue. Electrocautery involves the use of a Monopolar, high-frequency, electrical current to cut or coagulate tissue at temperatures ranging from 400° to 600°C. Dissection is performed with minimal intraoperative bleeding due to tissue coagulation and ablation. The technique shortens surgical time, however, increases pain, odynophagia, and results in increased risk of post-operative bleeding.

Coblation (Controlled Ablation)

This technology uses radiofrequency ablation for tissue removal. In this procedure, a special tool is used to create a high-frequency, low-temperature electrical field ranging from 40° to 70° C. Continuous saline delivery coupled to bipolar electrodes at the device tip generates a charged plasma field. This charged "glow discharge plasma" breaks down cellular bonds, dissolving it, and results in tissue ablation. The advantage of Coblation over traditional surgical techniques, such as electrocautery or scalpel, is that it causes less thermal damage to the surrounding tissues, resulting in a quicker recovery time and less pain for the patient. However, an increased risk for bleeding has been documented.

PEAK PlasmaBlade

The PEAK PlasmaBlade is a surgical device that uses bi-polar radiofrequency technology for cutting and coagulating tissues. It operates at significantly lower temperatures (40–170°C) compared to electrocautery, providing precision and minimal thermal injury to the patient. The advanced plasma technology reduces blood loss and results in improved surgical outcomes and quicker postoperative recovery. The device generates a high-frequency electrical field that ionizes the air, creating a plasma channel and removing tissue. The PlasmaBlade technology can work effectively even when submerged in liquids, providing consistent results. The PlasmaBlade technology is designed to provide improved surgical outcomes and faster recovery time for patients.

Harmonic

The Harmonic procedure uses the Harmonic scalpel, a surgical instrument that emits high-frequency ultrasonic vibrations, to cut and coagulate tonsil tissue simultaneously.

The Harmonic operating tip vibrates at 55 kHz allowing for tissues to be cut and coagulated simultaneously. Because no electrical energy is delivered directly to the tissue, the Harmonic generates little heat and thermal spread operating at less than 100°C. The procedure is performed as an outpatient procedure and has a quicker recovery time compared to traditional methods.

Microdebrider

Microdebrider is a surgical procedure that utilizes a microdebrider, a type of rotary shaver, to remove tonsil(s) tissue. The procedure involves cutting and removing the tonsil tissue with a high-speed rotating blade while suctioning away any debris. The tonsil is removed without disrupting the capsule, and hemostasis is performed using monopolar suction cautery on the tonsillar bed. This technique offers a minimally invasive option for tonsillar reduction and is typically performed as an outpatient procedure. It has been shown to be effective in treating tonsillar hypertrophy, with benefits such as less bleeding and pain compared to traditional methods.

1.1.3 Irreversible Electroporation (IRE)

Irreversible Electroporation (IRE) is a non-thermal ablation technique used to treat various medical conditions, primarily cancer and benign tumors. The procedure involves the use of high-voltage, low-energy electrical impulses to create permanent pores in the cell membranes, altering the cell transmembrane voltage which causes cell death (largely due to irrecoverable loss of homeostasis). The dead cells are then resorbed leading to tissue reduction.

IRE is used as a non-thermal ablation therapy with important advantages over the well-established conventional ablation methods. Compared to electrochemotherapy, the number of pulses and voltages in IRE ablation of tumors are significantly larger. The procedure is performed using a specialized device that delivers electrical impulses through electrodes placed on or near the target tissue. High voltage is used in IRE ablation of tumors. The spacing between the needle electrodes is 1.5-2 cm.

In IRE ablation, the cell death is predominantly a result of electroporation and not temperature increase. However, local heating of tissue does occur, especially near the electrodes and when large numbers of pulses are applied [3]. IRE technology provides several advantages as a non-thermal ablation technique: a) less collateral thermal damage, especially for vital nerves, vessels, and cavity structures; b) no heat sink effect, avoiding incomplete ablation due to the energy reduction caused by blood flow; and c) preservation of the extracellular matrix (ECM) scaffold, promoting rapid postoperative recovery.

Currently, IRE is mostly used for solid tumors such as liver cancer, pancreatic cancer, and prostate cancer and is considered an effective palliative treatment for advanced tumors near important ductal structures, such as large blood vessels, the intestines, bile ducts, or the urinary tract[4].

Rational of the Study

The purpose of the IRE System is to address the clinical need for reducing the volume of chronic symptomatic hypertrophic tonsil(s) while minimizing side effects and complications. Procedure

time will also be reduced. The IRE System is designed to be more comfortable for patients, as it employs a noninvasive procedure using a high voltage pulsed electric field to create irreversible nanopores in the cell membrane, leading to cell death and the reduction of tonsil volume. On basis of these finding and in view of the known safety profile (refer to Chen et.al[5]) and efficacy of current technologies, the purpose of the current study is to prospectively determine the efficacy and safety of the IRE System in tonsillar reduction.

2 The Investigational Device

2.1 Intended Use

Surgical Ablation of soft tissue.

2.2 Indication for Use

Indication for use in patients with chronic symptomatic tonsillar hypertrophy.

2.3 Device description

The IRE System is composed of a generator (console) and a passive handpiece (handpiece/applicator) aiming to deliver the high voltage electric power to the tissue by creating the suitable electric fields (E-field) to initiate the irreversible electroporation effect. The generator features a user-friendly interface that allows the user to monitor the system status and control parameters. A foot pedal connected to the generator is used to operate the system. The user interface (UI) is connected to a control unit that controls the high voltage (HV) power supply and is used to activate the system. The pulse generator is connected to the output module. The system consists of a tissue impedance measurement unit that allows the control unit to automatically adjust the output power (voltage and current) in accordance with tissue impedance and the impedance for the subsequent treatment (pulses). The handpiece is shaped as forceps with two distal medical-grade stainless steel electrodes that deliver the electrical power to the tissue.

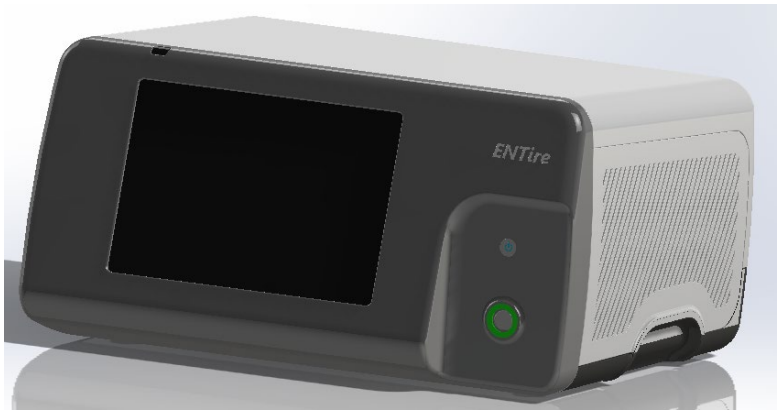


Figure 1: The IRE Console (Generator)

Figure 2: The configuration device (Handpiece)

2.4 The IRE System For Tonsillar Reduction Presents A Non-Significant Risk

The device complies with the definition of non-significant risk in accordance with FDA guidance under 21 CFR 812.3(m)

The device is IEC-60601 certified (General Safety, EMC, and Particular requirements for the basic safety and essential performance of high frequency surgical equipment and high frequency surgical accessories tests successfully).

Materials contacting the treated tissue biocompatibility, sterilization and cleaning process were evaluated in accordance with the applicable harmonized standards to comply with both USA FDA and EU CE regulations requirements.

The IRE device is designed with core safety, which is ensured via several aspects of its components:

- The IRE technology is a non-thermal RF technology enabling an isolated treatment targeted to the hypertrophic tonsil(s) only. The electrical energy is delivered only to the tissue exposed to the isolated electric field which is generated between the two electrodes. It should be noted that some local minor epithelium layer coagulation may occur.
- The energy delivered to the tissue is reliably controlled and limited. The system's control unit eliminates the risk of delivering unintended or incorrect energy levels to the patient by preventing overvoltage or overcurrent situations.
- The system's power output is an open output relay, meaning that the circuit is open and no current is flowing through the relay. Once the user indicates desired energy application to

the tissue, the relays are activated, and current flows through the relay. The system power output is always off in the event of a power failure or any other single fault occurrence.
- Output capacitors filter any high-power DC so only intended bi-phasal RF energy can be delivered to the target tissue.
- No bleeding or tissue epithelium layer perforation occurs, therefore the risk of biological contamination or excessive bleeding following treatment is minimized.

3 Study Design

This is a multi-center, prospective, open-label study with a before-after study design. The study is designed to evaluate the safety and efficacy of tonsillar reduction using an irreversible electroporation (IRE) system for the treatment of chronic symptomatic tonsillar hypertrophy.

The study will include a treatment and 4 visits at the clinic (1 screening visit and 3 follow up visits):

Screening will take place before treatment to determine the baseline measurements, demographic characteristics, and medical history.

After screening and receiving informed consent, participants will receive a single treatment for one or both tonsils using the IRE device. The patient will be monitored with by ECG during the treatment application and will be assessed at discharge.

Following treatment, the patient will be called daily for the first 7 days to assess their level of pain.

Post treatment follow-up visits will evaluate safety and efficacy of the treatment and will take place at 1 week (±3 days), 1 month (±7 days) and 3 months (±14 days) after the treatment session.

See Figure 3 for an illustration of the study design and Table 1 for a summary of the study procedures and Table 2 for the schedule of times and events.

This is a multi-center study where up to 40 patients meeting the inclusion criteria will be recruited, where a minimum of 22 patients will be recruited for the implementation of statistical analysis. Each center will enroll the patients for the study, at its own pace, until the total treated patient count will reach the study population.

It is noted that a successful patient is defined as a reduction in tonsillar mass of at least one treated tonsil, and in accordance with the study's primary endpoints. For statistical analysis, the study population may be considered by patient or per treated tonsil. Furthermore, the first 5 treated patients may be excluded from the statistical analysis.

Subjects must meet the eligibility criteria detailed in the protocol and sign the informed consent form prior to any study procedure.

Subjects will be screened before entering the study to determine the size of their tonsillar hypertrophy based on BGST.

Treatment will include one or more pulse sessions depending on the size of the treated organ (tonsil). Treatment duration will be up to 30 minutes (including anesthesia), according to the treatment protocol.

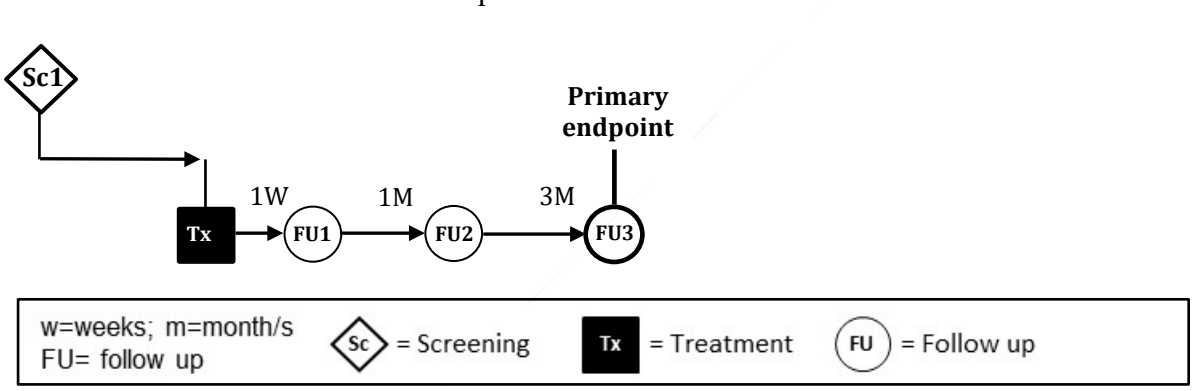
It is noted that the treatment procedure is expected to invoke minimal pain.

Patients will be given the following questionnaires to better understand their condition as outlined in Table 1: Snore VAS, Pain VAS and Tonsil and Adenoid Health Status Instrument (TAHSI).

Patient efficacy will be evaluated according to primary endpoints – BGST 3 months post-op compared to Baseline and a Pain VAS score at one-week post treatment to be non-inferior to literature. Secondary endpoints will be evaluated for supporting data in success evaluation. If possible, photographs will be taken during prescreening, and all follow up procedures as supporting data.

Patient safety throughout the study will be determined by the Investigator on site before and after treatment as well as by examining the post-treatment occurrences of complications and adverse events.

Figure 3: Study Design – IRE system- Totnsillar reduction



3.1 Study Endpoints

3.1.1 Primary Efficacy Endpoints

The primary objective of this study is to assess the performance of the IRE treatment on individual participants success rates when used as a treatment for tonsillar hypertrophy.

Individual patient success is defined as a reduction of tonsil size by at least one grade, according to the BGST, at the 3-month compared to Baseline, and a Pain VAS score at 1 week follow up visit to be non-inferior to literature.

3.1.2 Secondary Efficacy Endpoints

Additional objectives include assessment of secondary and informational outcome measures for individual patients undergoing IRE treatment for tonsillar hypertrophy.

Secondary endpoints are:

- A reduction in Snore VAS at 3 months post treatment compared to Baseline.
- Safety analyses as referred to in section 3.1.4

3.1.3 Additional Endpoints

- Primary and secondary endpoints at other evaluated time points.
- Medications - Medications associated with pain relief post treatment will be documented at baseline and updated at each evaluation (if applicable).

3.1.4 Safety Endpoints

The safety and risk profile of the IRE procedure will be evaluated with respect to overall incidence of adverse events (AE) (e.g., monitor morbidity and mortality after surgery; primary/secondary bleedings) as follows:

- The number of adverse events within 3 months from treatment; intraoperative and postoperative complications and treatment related adverse events.
- Physician assessment of the incidence of post-treatment reactions using a 0 to 3 grading scale (0=none, 1=mild, 2=moderate, 3=severe) following treatment and recorded any additional side effects.

Further categorized as serious and non-serious, device-related, non-device-related. Adverse events will be evaluated during the procedure, at all subsequent visits and any unscheduled visits.

3.2 Study duration

Duration of subject's participation: Up to 3.5 months from treatment to last post-op visit.
Study duration for entire study: Estimated to be 18 months from enrollment of first subject to the last post-op visit of the last subject.

3.3 Schedule of Times and Events

A summary of the required study visits, procedures, and assessments to be performed at each visit can be found in Table 1 and Table 2 below. Details of the procedures and assessments will be described subsequently in the protocol.

Table 1: Study Procedures - IRE- Tonsillar Reduction

Sc=screening; Tx=treatment; FU=follow up; D = days; W=weeks; M=months

Visit number (timepoints)	Screening (Baseline)	Treatment and Discharge	Post-Treatment Follow-up (office)		
	1 (0)	2 (After screening)	3 (2-3W)	4 (5-6W)	5 (13-14W)
Timeline (from Tx visit)		**0W**	**1W(±3D)**	**1M (±7D)**	**3M (±14D)**
Eligibility screen					
Inclusion/Exclusion criteria	X				
Informed consent	X				
Baseline information	X				
Oral Exam	X				
BGST	X				
Snore VAS	X				
TAHSI	X				
Tonsil(s) photography (optional)	X				
Interventions					
IRE Treatment (Tonsillar Reduction)		X			
Assessments					
Oral Exam		X[2]	X	X	X
BGST			X	X	X (*)
Pain VAS		(**)	X (*)	X	X
Snore VAS			X	X	X
TAHSI			X	X	X
Tonsil(s) photography (optional)			X	X	X
Participation sign-off					X

(*) Primary endpoint

(**) For the first 7 days following treatment, the patient will be called daily and asked about levels of pain.

[2] At discharge

Table 2: Times & Events – IRE Tonsillar Reduction

Details	
VISIT 1: Screening Day 0	Compliance with study criteria, informed consent, baseline information (including medical history and demographic information), oral examination, Brodsky Grading System, Snore VAS, TAHSI and tonsil(s) photography (optional).
VISIT 2: Treatment After Screening	IRE treatment, AE, and other safety evaluations.
Discharge: 1-2W	Oral Examination, and other safety evaluations.
VISIT 3: Follow-Up 1W post-op (±3D)	Oral exam, Brodsky Grading System, Pain VAS, Snore VAS, TAHSI, tonsil(s) photography (optional) and other safety evaluations.
VISIT 4 – Follow Up 1M post treatment (±7D)	Oral exam, Brodsky Grading System, Pain VAS, Snore VAS, TAHSI, tonsil(s) photography (optional) and other safety evaluations.
VISIT 5 – Follow Up 3M post treatment (±14D)	Oral exam, Brodsky Grading System, Pain VAS, Snore VAS, TAHSI, tonsil(s) photography (optional), other safety evaluations and participation sign-off.

4 Study Population and Subject Selection

4.1 Source and Sample Size

This is a multi-center study where up to 40 patients meeting the inclusion criteria will be recruited, where a minimum of 22 patients will be recruited for the implementation of statistical analysis. Each center will enroll the patients for the study, at its own pace, until the total treated patient count will reach the study population.

It is noted that a successful patient is defined as a reduction in tonsillar mass of at least one treated tonsil, and in accordance with the study's primary endpoints. For statistical analysis, the study population may be considered by patient or per treated tonsil. Furthermore, the first 5 treated patients may be excluded from the statistical analysis.

The subjects will be recruited by the Investigator(s) from within the investigator's subject population and if needed from the general population by use of an Ethic Committee (EC) approved advertisement.

4.2 Eligibility

Each subject will be evaluated by the Investigator to assess his/ her suitability for entry into this study according to the criteria below.

4.2.1 Inclusion Criteria

Subjects must meet all the following inclusion criteria to be entered into the study:

- Age 18 – 70 years
- Tonsillar Hypertrophy of grade 2 or higher on the BGST.

4.2.2 Exclusion Criteria

Any of the following will exclude the subject from the study:

- Age below 18 years.
- Patients with a pacemaker or similar electro stimulator.
- Patients for whom the anesthesia involves high risk.
- Epilepsy or other condition involving convulsions.
- Inability to give informed consent and to complete self-reported questionnaires.
- Patients with an inability to cooperate for treatment and follow-up.
- Severe heart disease.
- Pregnancy or breastfeeding.
- Significant systemic illness (e.g., cancer, severe autoimmune disease, neurological disease).
- Bleeding diathesis.
- Patients suffering from obesity as indicated by a body mass index (BMI) > 32kg/m2.
- Known or suspected complications for any general or local anesthetic agents and/or any antibiotic medications.

4.3 Subject Withdrawal and Replacement

Subjects may withdraw their consent to participate in the study at any time without prejudice as written in the informed consent form.

The investigator(s) may withdraw a subject if, in his clinical judgment, it is in the best interest of the subject if the subject cannot comply with the protocol or if the subject is unable to adhere to appointments. If a subject drops out of the study or is withdrawn from the study, the Early Discontinuation or Withdrawal CRF form should be completed. Reasonable effort should be made to contact any subject lost to follow- up during the study to complete assessments and retrieve any outstanding data and study medication/supplies. The records of subjects who terminate prior to completing the study will be retained and the reason for termination will be documented. The Sponsor must be notified of all withdrawals within 7 working days.

4.4 Subject Compensation

Subjects will not pay for any office visits, examinations, and procedures as part of this clinical study.

5 Study Procedures

5.1 Screening Visits

5.1.1 Subject Enrollment

- During the screening visit, the study investigator, and/or his designee (both referred to as the Investigator), will screen the subject for eligibility to participate in the clinical study using the Inclusion/Exclusion criteria. The study Investigator will obtain an informed consent form from the subject, clearly indicating his/her understanding of the requirements and risks involved with study participation and other applicable treatment options.
- For women of child-bearing age, Investigator will inform the patient that she must not be pregnant and is not planning to be pregnant for the study duration.
- If the subject has met the preliminary study criteria, he/she will be enrolled to the study.

5.1.2 Subject Identification

At enrollment each subject will receive a unique identifying number that will be composed of a consecutive number and his/her initials. This unique identifier will be used throughout the entire study and will be entered in the subject's Case Report Form (CRF), questionnaires and photographs (as applicable).

5.2 Patient visits

Subjects will receive 1 treatment. Patients will undergo a tonsil IRE treatment. The duration of the treatment including evaluations, treatment and subject safety assessment is estimated to be up to 30 minutes. Clinic visits (pre-op and post-op) are estimated to be up to 45 minutes.

Expected short term responses to treatment may include pain, and possible slight bleeding due to minimal mechanical damage to the treated organ.

5.2.1 Pretreatment Procedures

5.2.1.1 ***Patient preparation prior to treatment***

Each patient will be evaluated by the Investigator to assess his/ her eligibility for this study according to the Inclusion/ Exclusion criteria. The Investigator will provide the patient with information about the treatment, involving its purpose and expected outcomes including any potential side effects or risks. After the patient signs an informed consent for the treatment, their medical and medication history will be reviewed, their baseline measurements will be taken, and they will undergo an oral examination (including tonsillar photography, as applicable) and tonsillar grading according to BGST. Prior to treatment, each patient will fill out a Snore VAS and TAHSI to evaluate their baseline. If applicable, any general analgesics and antibiotics taken prior to the procedure will be recorded.

BGST is a common method for the evaluation of the tonsil(s) airway obstruction as presented by Brodsky[6]. The BGST is based on the following grading system:

The grading system consists of a scale from 0 to 4. Grade 0 denotes a complete absence of obstruction on the oropharyngeal airway. Grade 1 is defined as tonsil(s) that sit just outside of the tonsillar fossa with obstruction of less than 25% of the airway. Grade 2 Tonsil(s) are readily seen in the airway- 25 to 50% of the airway is obstructed. Grade 3 Tonsil(s) denote a 50 to 75% obstruction of the airway. Grade 4 represents Tonsil(s) involving a greater than 75% obstruction of the airway.

5.2.1.2 ***Digital photography (optional)***

Using an endoscopic system is optional for this research to obtain tonsil(s) grade assessment using BGST; they may also be used by the Sponsor for future educational and marketing purposes.

Photographs will be taken as part of prescreening and follow-up visits of 1 week, 1- and 3-months.

Tonsil photos should be taken in the clinic under procedure-controlled conditions using an endoscopic system, preferably a rigid 4mm endoscope diameter 0°. The pictures are required to estimate tonsil(s) characteristics such as size, shape and morphology.

For consistency purposes, the same person should ideally take all study photographs per subject.

Photographs must be taken using a tongue press and by placing the endoscope at the base of the teeth.

The digital files should follow a consistent standard naming scheme, for example:

XXX_YY_VV_Date

when:

- XXX – Subject's study ID number
- YY – Subject's initials

- VV – Visit information: Sc= screening; FU1= post treatment follow up after 1 week; FU2= post treatment follow up after 1 month; FU3= post treatment follow up after 3 months.
- Date – Date of photographing.

5.2.2 Treatment procedure

- The tonsil(s) will be treated with the IRE System. The treatment duration will be up to 30 minutes.
- Subjects will be positioned during treatment in a manner that will enable the best access to the treatment area - as dictated by the physician.
- The subject's cardiac rhythm will be monitored during treatment application by ECG.
- The treatment parameters specific to the subject will be documented in the Case Report Form (CRF). A discharge CRF will be filled out upon release from the medical facility.

5.2.2.1 *Treatment*

A detailed description of the treatment can also be found in the IRE System user Manual.

The following is a brief description of the treatment procedure:

- Subjects will be treated under general anesthesia, sedation, or local anesthesia- as determined by the primary investigator.
- Subjects will be positioned during treatment in a manner that will enable the best access to treatment area.
- Treatment electrodes should be placed in full contact, perpendicular to the tonsil(s), with light to moderate pressure applied to achieve the anticipated electrical conductivity between the device electrodes and the treated tonsil(s).
- Pressing the foot pedal, or the touch screen of the IRE System (GUI), a single treatment dose will be delivered through a series of brief bursts of pulses (each pulse will last a few microseconds).
- The patient's cardiac rhythms will be monitored by ECG during the application of the treatment.
- Treatment may be repeated up to 6 times at each treated site (treatment may be done at several sites on the tonsil(s) surfaced, according to the need, as determined by the Investigator).

5.2.3 Post-treatment procedures

5.2.3.1 *Subject post treatment care*

There are no relevant post care and interventions that are permitted or prohibited post care. If relevant, the use of analgesics and antibiotics will be monitored.

5.2.3.2 *Home instructions*

- Subjects should be aware that post treatment discomfort is possible.
- Subject should be made aware that they will be called for the first 7 days following treatment in order to rate their pain levels.

5.3 Follow-up visits

The procedures required at the follow up visits are the following:

5.3.1 Oral Assessment

An oral assessment will commence at the screening visit, at patient discharge after treatment, and at every follow up to examine oral cavity. Evaluation of the healing process and any potential complications following the surgery will be documented in the CRF. The assessment typically includes a visual examination of the tonsillar bed to check for signs of bleeding, infection, or other complications. The Investigator may also check the patient's oral and pharyngeal mobility, ask about any pain, or discomfort, and assess the patient's ability to swallow and eat. An endoscope and a tongue depressor will be used to visualize the tonsil(s) and assess their size and appearance (grading will be documented in the CRF by BGST) and tonsil(s) will be photographed during the oral exam (optional).

5.3.2 Safety

See Section 6.2

5.4 Study Completion

The study completion CRF will be evaluated after the 3 months post-op visit. The study's success will be evaluated after assessing the patients' endpoints – see Section 6.

6 Evaluations

6.1 Efficacy Evaluations

6.1.1 Clinical evaluation

Efficacy:

Effectiveness analysis will be composed of the assessment in reduction of tonsillar hypertrophy size as demonstrated by BGST method and post procedure related pain as compared to available literature for other surgical treatment for hypertrophic tonsillar reduction. The following are the measures of assessment used in the study.

Brodsky Grading System for Tonsils: The BGST is a method for categorizing the severity of tonsillar hypertrophy, which refers to an enlarged tonsil. The system assigns a score to the tonsil(s) on a scale of 0 to 4 based on the visibility of the tonsil(s) relative to the palatine arch and the uvula when viewed from the back of the throat. Grading identifies the severity of the airway obstructions by the tonsillar hypertrophy based on their degree of obstruction in the oropharynx. Studies have shown that as Brodsky grade increases the oropharyngeal width decreases where an increase in oropharyngeal width. A primary endpoint in this study is the reduction by at least one grade in the BGST.

Pain VAS: Visual Analog Scale Pain Score (Pain VAS) a horizontal 10 cm visual analog scale (VAS) ranging from 0 “No Pain” to 10 “Worst Pain Imaginable”, will be used to measure tonsil reduction pain associated with the procedure. Scores are obtained by measuring the distance in

cm from the left origin of the line (0) to the point indicated with a vertical slash placed by the participant to indicate their current level of pain of the tonsil treated and around the oral cavity.

Snore VAS: Snoring is often associated with tonsillar hypertrophy, as enlarged tonsils can partially obstruct the airway and cause vibration of tissues in the throat, leading to snoring. Snore Visual Analog Scale (Snore VAS) is a tool used to assess the severity of snoring. The Snore VAS consists of a 10 cm line with two anchored ends, one labeled "Never" and the other labeled "All the time." The patient or a bed partner is asked to rate the severity of the snoring by marking a point on the line. The distance from the "no snoring" end to the marked point is measured and used as a numerical score to quantify the intensity of the snoring.

The Tonsil and Adenoid Health Status Instrument (TAHSI): is a standardized tool for evaluating the health status of tonsils and adenoids in adult patients. It consists of a 18-question questionnaire and a clinical assessment component. The TAHSI is designed to provide a comprehensive assessment of the severity of symptoms and their impact on quality of life. Each question is scored on a scale of 0 to 4, with 0 indicating no symptoms and 4 indicating severe symptoms. The total score is the sum of all the individual question scores and can range from 0 to 72. A higher total score indicates a greater severity of symptoms and a greater impact on quality of life.

6.2 Safety

Safety measures include documenting the incidence of treatment-related immediate, short term, and long-term treatment response. Adverse events are defined in this protocol under Section 88, and include anticipated side effects of the procedure. These events will be tracked by the clinical site and will include subject-reported events. The events will be attributed as being not related or possibly to definitely related to the device or procedure by the investigator. The proportion of subjects who prematurely terminate from the study due to a treatment-related AE and treatment-related pain ratings will be documented as well.

6.2.1 Immediate/short term response (up to 1 week)

Expected post treatment immediate response including sore throat and discomfort will be documented post treatment by the Investigator during discharge in the CRF as treatment site pain.

Sore throat and discomfort are anticipated responses that may or may not appear several days after the treatment and is expected to disappear up to one week post treatment. This information will be documented under Subject's evaluation as pain in the Pain VAS at the 1-week post-op visit.

6.2.2 Long term side effect and AEs – incidence and severity (also see Section 8)

Long term side effects and adverse events will be assessed throughout the duration of the study. The reaction will be evaluated on-site and include the following clinical outcomes:

- Numbness
- Infection
- Presence of prolonged erythema/edema/burning sensation
- Ulceration

- Other

AEs severity and relation to the treatment will be assessed and documented. For a detailed description see Section 8.1.

Report of adverse events by subjects and the Investigator will be documented in the designated section in the CRF of the specific visit in which the event was observed as well as in the separate Adverse Events form.

7 Study Analysis Plan

7.1 Study Design and Objectives

This is a multi-center, prospective, open label study with a before-after study design. The study is designed to evaluate the safety and efficacy for the treatment of tonsillar reduction of chronic symptomatic hypertrophic tonsil(s) using the IRE System.

7.2 Study Endpoints

7.2.1 Primary endpoint

- Reduction of tonsil(s) size in accordance with the BGST by at least one grade at 3 months compared to the Baseline.
- Pain VAS at 1 week follow up visit to be non-inferior to literature.

7.2.2 Secondary endpoints

- Snore VAS reduction at 3 months compared to the Baseline. To evaluate procedure-related safety.

7.2.3 Additional endpoints

- Primary and secondary endpoints at other evaluated time points.
- Medications - Medications associated with pain relief post treatment will be documented at baseline and updated at each evaluation (if applicable).

7.2.4 Safety Endpoints

The safety and risk profile of the IRE procedure will be evaluated with respect to overall incidence of adverse events (AE) (e.g., monitor morbidity and mortality after surgery; primary/secondary bleedings) as follows:

- The number of adverse events within 3 months from treatment; intraoperative and postoperative complications and treatment related adverse events.
- Physician assessment of the incidence of post-treatment reactions using a 0 to 3 grading scale (0=none, 1=mild, 2=moderate, 3=severe) following treatment and recorded any additional side effects.
- Further categorized as serious and non-serious, device-related, non-device-related. Adverse events will be evaluated during the procedure, at all subsequent visits and any unscheduled visits.

7.3 Success/Failure Criteria

Determinations of the overall success of treatment will be based on two levels: (1) the individual participant level and (2) the overall treatment success. Each level has its own criteria for success.

7.3.1 Participant Success

The primary outcome success measure for a participant in this study is based on a decrease in the BGST after the treatment as compared to the baseline as well as Pain VAS scores.

The success criteria are defined as follows:

- Reduction by at least one grade in the BGST grade at the 3-month post treatment visit compared to the baseline.
- Pain VAS score at 1 week follow up visit to be non-inferior to literature.

It is noted that a successful patient is defined as a reduction in chronic tonsil hypertrophy of at least one treated tonsil, and in accordance with the study's primary endpoints.

7.3.2 Participant Failure

A participant will be considered a failure if at the 1-week Pain VAS endpoint evaluation or at the 3-month BGST endpoint, patient success had not been attained.

7.3.3 Study Success

The study will be considered a success if 75% of total participants reach a successful outcome, as defined in section 7.3.1.

Literature demonstrates a study success where approximately 75% of patients achieve tonsillar reduction via ablation treatment with an average volume reduction of the tonsil/s in treated adult patients is between 30-50%[7,8,9,10,11].

- Studies have demonstrated that BGST correlates to tonsil volume where a reduction of one grade correlates to 30-40% volume reduction depending on the initial grade.
    - The mean tonsil volume of grades 1, 2, 3, and 4 was 2.58±1.15, 4.33±1.99, 6.58±2.69, and 9.33±1.15 ml respectively[12].

This study aims to be non-inferior to current modalities for tonsil reduction with a similar study success of 75%.

- As this is a non-invasive procedure (no surgical incisions, no bleeding, and a lowered expected rate of complications) a one grade reduction in BGST is considered clinically significant.
- A study success of 75% with non-inferiority margin of 20% is taken to be clinically significant.
- For statistical analysis, the study population may be considered by patient or per treated tonsil.
- The first 5 treated patients may be considered as physician's learning curve.

7.3.4 Study Hypothesis

In this study we will assess the following hypothesis:

IRE System will showcase non-inferiority in efficacy and safety for treatment of chronic symptomatic tonsillar hypertrophy based on the outcome being a significant clinical benefit (according to the study's primary endpoints), and when applicable, non-inferiority efficacy and safety of the IRE System treatment compared to other approved technologies, through review of available relevant literature.

7.3.5 Sample Size Estimation

Sample Size Rationale: The current study aims for the initial safety and efficacy evaluation of the technology.

The multi-center study population will include up to 40 patients, where a minimum of 22 patients will be included for the implementation of statistical analysis where, a one-sided (lower) 95% confidence interval for a single proportion will range from 0.55 to the sample proportion of 0.75.

For statistical analysis, the study population may be considered by patient or per treated tonsil. Furthermore, the first 5 treated patients may be excluded from the statistical analysis.

7.3.6 Randomization and Blinding

Not relevant. The study design is single arm, non-blinded.

7.3.7 Full analysis set (FAS)

The full analysis set (FAS) includes all subjects who underwent an IRE treatment with the study device and at least the 1-month post-op visit.

7.3.8 Per-Protocol (PP)

The per-protocol analysis set (PP) will consist of only patients who completed the study as intended and adhered to the protocol. PP analysis set will consist of those patients who received IRE treatment and attended all follow up visits as well as filled out the patient's Pain VAS, Snore VAS and TAHSI questionnaires.

7.3.9 Statistical Analysis of Analysis Sets

The FAS analysis set will serve as the main set for safety assessments.

The primary efficacy assessment will be performed on the PP analysis set and as supportive analysis, on the FAS.

For statistical analysis, the study population may be considered by patient or per treated tonsil. Furthermore, the first 5 treated patients may be excluded from the statistical analysis.

7.4 Statistical Analysis

7.4.1 General Considerations

Baseline demographic and other baseline characteristics, together with safety analyses will be performed on all treated subjects. Baseline values are defined as the last valid value prior to first treatment.

Statistical analyses of safety and secondary endpoints efficacy will be mainly descriptive in nature. Continuous variables will be summarized by a mean and standard deviation.

Based on final population size, statistical analysis will be performed on the primary endpoint as compared to literature, where a one-sided (lower) 95% confidence interval for a single proportion will range from 0.55 to the sample proportion of 0.75. The confidence interval was calculated using the Clopper-Pearson Exact Method.

7.4.2 Demographic and Other Baseline Variables

Demographic and baseline condition related characteristics will be tabulated. Continuous variables will be summarized by a mean, standard deviation, minimum, and maximum, and categorical variables by a count and percentage.

7.4.3 Disposition of Subjects

The number of subjects screened and reasons for screening failures will be presented.

The numbers of subjects who were enrolled will be provided, as well as the reasons for all enrollment discontinuations, grouped by major reasons (e.g., lost to follow-up, adverse event, etc.). A list of discontinued subjects, protocol deviations, and subjects excluded from the analyses will be provided as well.

7.4.4 Efficacy Analysis

Efficacy analysis will be composed of the assessment in reduction of tonsillar hypertrophy at 3 months post-op visit compared to Baseline as well as post-op. pain evaluated one week after treatment. Hypertrophic tonsillar reduction will be assessed using the BGST.
Other values that may demonstrate the effectiveness of the IRE treatment include a reduction in snoring as assessed by Snoring VAS.

7.4.5 Safety Analysis

Safety evaluation will be based on the number of reported complications and adverse events (e.g., numbness, infection, etc.).

- The number of adverse events (e.g., numbness, infection, etc.)
- Physician assessment of the incidence of post-treatment reactions using a 0 to 3 grading scale (0=none, 1=mild, 2=moderate, 3=severe) following treatment and recorded any additional side effects.
- Further categorized as serious and non-serious, device-related, non-device-related. Adverse events will be evaluated during the procedure, at all subsequent visits and any unscheduled visits.

7.4.6 Pooling

The data analysis for this study will involve pooling data from multiple study sites. The study will be carried out using a standardized protocol across all sites, ensuring uniform training of site investigators and personnel. Additionally, central data management and monitoring will be applied equally at each site. These measures aim to ensure the consistency and quality of the data collected from all sites, allowing for effective pooling and analysis of the data.

7.4.7 Handling of Missing Data

Missing data will not be included.

8 Adverse Events

8.1 Adverse Events Definitions

In this study, an Adverse Event (AE) is any undesirable clinical occurrence (sign, symptom, illness, or other medical event), that appears or worsens during the clinical study, which requires medical treatment or intervention to a subject, whether it is considered to be device related or not. If an adverse event occurs, the first concern will be the safety and welfare of the subject. Appropriate medical intervention will be made.

Any AE or complication reported by the subject or observed by the Investigator that occur during or after treatment and until the last post-op visit (3 months), will be recorded in the medical record or source document and on the Case Report Form. The Investigator will determine if the AEs are device related or procedure related. This assessment shall include the following:

8.1.1 Onset date and resolution date

8.1.2 Frequency

8.1.3 Treatment for the AE and outcome

8.1.4 Severity

Each AE should be assessed for its severity, or the intensity of an event experienced by the subject.

Mild: Awareness of a sign or symptom that does not interfere with the subject's activity or is transient resolved without treatment and has no sequelae.

Moderate: May interfere with the subject's usual activity and require additional intervention and/or treatment and may have additional sequelae.

Severe: Significant discomfort to the subject and/or interferes with the subject's activity. Additional intervention and or treatment are necessary. Additional sequelae occur. Severe is used to describe the intensity of an event experienced by the subject.

8.1.5 Serious Adverse Events (SAE)

NOTE: The term serious is not synonymous with severity, which may be used to describe the intensity of an event experienced by the subject. An AE that does not meet any of the criteria below will be classified as non-serious.

A serious AE is any event that:

- Results in, or contributes to a death.
- Is immediately life-threatening (injury or illness).
- Results in hospitalization, or prolongs an existing hospitalization.
- Results in permanent impairment of body structure or function, or in persistent or significant disability/incapacity.
- Results in an injury that requires medical intervention to prevent permanent impairment of body structure or function.
- Is a device malfunction or deterioration in the characteristics and/or performance of the device that results in death or serious deterioration in health.
- Is a device malfunction or deterioration in the characteristics and/or performance of the device that, if it were to occur again, could result in death or serious deterioration in health.
- Results in a congenital anomaly or birth defect.
- Is any medically significant injury, event or experience that requires medical/surgical intervention to prevent one of the outcomes listed above.
- Results in additional surgery or intervention related to the procedure.

8.1.6 Relationship of AE to the Device (Technology)

Each AE should be assessed for its relationship to the device or procedure as identified as follows:

Device: This category should be restricted to adverse events directly attributable to the effect of the device

Procedure: A procedure is any activity that supports the usage of the device

Use the following categories for assigning the certainty of the relatedness:

Definitely Related: An AE is definitely related if it is obvious, certain or there is little doubt regarding the relationship.

Probably Related: An AE is probably related if it cannot be explained by a concomitant illness or by other medicinal products.

Possibly Related: An AE is possibly related if it is capable of being related but relatively unlikely.

Not Related: An AE is not related if it is determined that there is no plausible association.

Unknown: Use this term if there is insufficient information to determine if the AE is related to the device or procedure.

8.1.7 Anticipated Outcome Related Adverse Events

Potential risks associated with the use of the IRE System and the associated general or local anesthetics are listed below. Participants will be monitored closely as part of this study to allow for early detection of potential problems and prompt treatment (if required).

Possible adverse events may include, but are not limited to:

- Reactions to anesthetics.
- Bleeding (other than bleeding greater than anticipated).
- Infection.
- Pain or burning sensation.
- Local burns.
- Arrhythmia.
- Injury to anatomical structure.
- Hematoma.
- Hemorrhage.
- Severe muscle contraction during procedure;
- Venous Thrombosis.
- Ablative Injury.
- Procedural Complication.
- Inflammation/ generalized redness in the treated area;
- Fever.
- Shock.
- Allergic reaction (itching, redness, or rash);
- Charring.
- Scar formation.
- Sensory changes at treatment site.
- Temporary numbness/tingling.

In case of any of the occurrence of any side-complication or adverse effect, it is imperative to consult a physician within a short period.

Any anticipated AE that occurs at any time during or after the use of the study device must be reported by the Investigator to the Sponsor.

8.1.8 Unanticipated Adverse Device Effects

An unanticipated adverse device effect as defined by the Federal Regulations [21 CFR 812.3(s)] is "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects." From a practical perspective, an unanticipated adverse device effect means a serious adverse event that is not listed in the device labeling, or the frequency or severity is greater than reported in the device labeling.

In the event of a serious (or unanticipated) adverse event, the Investigator will immediately notify the Sponsor monitor by telephone. If such an adverse event is being reported after normal

working hours, the Investigator will leave a voice message with accompanying report of the AE.

8.1.9 Diagnosis of Adverse Event

There should be an attempt to report a "diagnosis" rather than the individual signs, symptoms and abnormal values associated with the diagnosis. However, a diagnosis should be reported only if, in the Investigator's judgment, it is relatively certain (i.e., definite or possible). Otherwise, individual signs, symptoms and abnormal values with outcomes as described in Section 8.1.7 should be reported as adverse events.

8.1.10 Pre-existing Conditions

A pre-existing condition should not be reported as an adverse event unless there has been a substantial increase in severity or frequency of problems, which has not been attributed to natural history.

8.2 Reporting

8.2.1 SAE Reporting

All SAEs, whether deemed expected or device related, must be reported to the Sponsor immediately or within 24 hours by telephone (see below). A written report must follow within five (5) working days and is to include a full description of the event and sequence. The SAE report (initial and/or follow up) should be sent via e-mail to the Sponsor at info@ent-ire.com (secondary). Study personnel must forward follow-up information and complete event report to the Sponsor as the event continues and/or subsides/resolves, or in the case of permanent impairment, until the event stabilizes, and the overall clinical outcome has been ascertained.

The e-mail confirmation should be filed in the Investigator Site Binder.

The procedures for notification of suspected serious unexpected adverse reactions (SUSARs) shall be carried out in accordance with local rules and regulations. Serious adverse events should be reported by the Sponsor to the EC according to local requirements. Subjects who have had an SAE during or immediately after the study procedure must be followed clinically until all parameters have either returned to normal or have stabilized or are otherwise explained and/or resolved.

Any newly emergent SAEs, after completion of study procedure follow up, that is considered to be related to the study procedure, should be recorded and reported immediately. The post-study period for the purpose of SAE reporting is routinely up to 30 days following the last study visit or until SAE is resolved or stabilized. It is the responsibility of the Investigator to inform the EC and national authority of the SAE as required by local laws and regulations.

In addition to reporting adverse events within the context of this clinical study, 21 CFR Part 803 Medical Device reporting requirements and any applicable local device reporting requirements will be followed.

8.2.2 Device Malfunctions/Medical Device Reporting

Each device failure/adverse event will be assessed for possible reporting as a Medical Device Report (MDR), and a determination will be made in accordance with the Sponsor's standard operating procedure. MDRs will be reported in accordance with 21 CFR 803 and the local reporting requirements.

The Investigator will report the device malfunction to the EC according to the local country regulation according to regulatory requirements.

8.3 Risk/ Benefit Analysis

8.3.1 Risks

The potential risks for adverse effects of the treatment procedure include but are not limited to burns, excessive edema or erythema, infection, and scarring, as detailed above in Section 6.2.1.

8.3.2 Anticipated Benefits

Potential benefits may include but are not limited to short treatment time, substantial reduction of bleeding (if any), and fast healing due to the nature of the IRE ablation process.

9 Administrative Procedures

9.1 Investigator Selection

The Investigator must be of good standing as an Investigator and knowledgeable in relevant areas of clinical research to ensure adherence to the requirements of the protocol, including the protection of human subjects. Other site personnel must have appropriate research experience and infrastructure to ensure adherence to the protocol and enrollment of sufficient numbers of evaluable subjects. The curriculum vitae (CV) of the Investigator will be maintained in the Sponsor files as documentation of previous medical training. The Principal Investigator will sign the signature page of this protocol, agreeing to comply with all applicable government regulations and the requirements of this study.

9.1.1 Site Staffing and Responsibilities of Study Personnel

The Principal Investigator (PI) is the lead researcher and has the ultimate responsibility for ensuring that the study is conducted ethically and according to the protocol, regulatory requirements, and Good Clinical Practice (GCP) guidelines. The PI is responsible for supervising the study staff, ensuring that s/he has satisfactory and qualified staff to conduct the clinical study, and that all study-related tasks have been appropriately delegated and documented.

Treating physician (Investigator(s)) – The treating physician will perform the procedure and post procedure assessments. The treating physician must be a medical doctor with experience in ENT procedures and trained in administering the IRE System and procedure.

9.2 Ethic committee Approval

This clinical study will be conducted according to all applicable regulations under 21 CFR, the Medical Device Directive and in accordance with the ICH Good Clinical Practice and local laws and regulations relevant to the use of medical devices.

An Ethical Committee (EC or IRB) will approve the clinical study protocol prior to study initiation. Approval will be indicated in writing with reference to the final protocol number and date.
Details regarding the EC/IRB's constitution including the names of its members, their qualifications and what function they perform on the board (e.g., chairman, specialist, lay-member) will be made available to enable the Sponsor and the Investigator to conform to regulations governing research on experimental devices.

9.3 Case Report Forms/Data Collection

This study can be performed only by collecting and using subject personal health information. The study records will be kept as confidential as possible under local, state and federal laws.

The Investigator is responsible for completely and accurately recording study data in the appropriate sections of the CRFs (including patient questionnaires) provided by the Sponsor. The CRFs must be signed by the Investigator or by his/her authorized person as designated in the Signature Authorization Log.

Data recorded on the CRF and photographs (as applicable) will serve as the “study data”.

The monitor will ensure the quality of data recording at the investigational site by comparison to supporting source documents during periodic site visits. Adherence to proper recording of information as well as assuring that corrections are being made will also be addressed during these periodic visits.

When the final study data is prepared for publication and other reports, subject identity will not be revealed. If they withdraw the authorization, the information collected up to that time may still be used to preserve the scientific integrity of the study.

9.4 Required Documentation

Prior to starting the clinical study, the following documents must be submitted or returned to the Sponsor by the Investigator:

- Signed Clinical Trial Acknowledgement for the protocol.
- Signed Clinical Study Agreement.
- Curriculum Vitae of the Principal Investigator.
- Signed Financial Disclosure Statement for each Investigator.
- Ethic Committee Assurance of Compliance form or equivalent.
- Written approval from the Ethical Committee of both the protocol informed consent form and subject questionnaires.

9.5 Device Use/Accountability

The evaluation site personnel will maintain records of the model and serial number of the devices (if appropriate) used for each treatment during the conduct of the study. The device to

be used in this study will be loaned to the clinic only for the purpose of herein detailed procedures and will be returned to the Sponsor following the completion of the treatment phase. Any additional equipment (non-disposable) dedicated to the clinical study that was provided by the Sponsor will be returned to the Sponsor at the end of the study.

9.6 Training Requirements

Both the Investigator and the Sponsor, prior to any independent use of the device, will agree upon the Investigators' training requirements. Site initiation training will occur prior to the first procedure at a site, as necessary, to ensure compliance with the protocol and regulatory requirements, as well as to ensure accurate data collection. Prior to the study, the Sponsor will ensure that each Investigator has received in-depth training on the use of the IRE System (generator and handpiece) and the procedure. Site training will include a detailed review of this protocol, use of the IRE System, CRF completion instructions, adverse event reporting, product handling and inventory, monitoring logistics, and regulatory requirements.

9.7 Modification of Protocol

The protocol may be amended with the agreement of the Sponsor and upon notification of and approval by the EC or other relevant ethic committee.

Investigators should review the contents of this protocol. Subsequent alterations should only be made in written conjunction with the Sponsor and the EC approval.

Medically significant amendments to the protocol (e.g., changes that increase the risk or the inconveniences for the subject, inclusion of new categories of subjects, etc.) must be approved by the local IRB or other relevant Ethic Committee prior to implementation.

9.8 Data Retention/Archiving Data

The Investigator must keep all documents of the trial at least 15 years after the clinical trial or according to the current local country regulations.

9.9 Site Monitoring

The study monitors are designated as agents of the Sponsor and are assigned to oversee the conduct and progress of the study and to be the principal communication link between the Sponsor and Investigator. The study monitors will be involved in monitoring of site and records, to ensure continued compliance with the protocol and adequacy of the Investigator and the facility to carry out the study.

The study will be monitored by representatives of the Sponsor by telephone, in writing and during on-site visits. At a minimum, site visits will be scheduled prior to the initiation of the study, on the occasion of the initial use of investigational devices, and at the end of the study. The purpose of site visits will be to ensure compliance with the investigational plan, to ensure appropriate use of investigational devices, and to inspect and retrieve study data.

A separate Clinical Monitoring Plan was put in place.

Personnel from the following organizations may also examine the study records: personnel associated with this study (including monitors and auditors), the EC, and regulatory agencies,

such as the United States Food and Drug Administration (FDA). Because of the number of individuals who may see these records, absolute confidentiality cannot be guaranteed.

9.10 Termination of Study

The Sponsor reserves the right to discontinue the study at any time for administrative purposes or other reasons. Written notice of study termination will be submitted to the Investigator in advance of such termination. Termination of a specific site can occur because of (but not limited to) inadequate data collection, low subject enrollment rate, achievement of the total enrollment, or non-compliance with the protocol or other clinical research requirements.

9.11 Reporting Requirements

The Investigator must promptly report to the Sponsor any withdrawal of IRB or other relevant Ethic Committee approval at the site.

Additional Investigator reporting requirements include:

- Notify the Sponsor or its designee with a report of any serious adverse device effect, whether anticipated or unanticipated, that occurs during the study as soon as possible, but in no event later than 10 working days after the Investigator first learns of the event. This report is to include a description of the event, subsequent treatments, clinical outcomes, and outcome diagnoses. If the site personnel are not sure whether an event meets these criteria, they should call the clinical monitor.
- Notify the Sponsor or the Sponsor’s designee and the IRB or other relevant Ethic Committee immediately (within 24 hours) if an emergency situation arises in which the subsequent treatment, in the best interests of the subject, requires a deviation from the protocol. This should be followed with written confirmation that describes the emergency action and outcomes, to the Sponsor and the IRB or other relevant Ethic Committee within 5 working days.
- Report adverse events in accordance with 21 CFR 803 and local regulation.
- Submit regular progress reports to the Ethic Committee and Sponsor or the Sponsor's designee, as requested by the Investigators or IRB or other relevant Ethic Committee.
- Submitting a final report on the study to the IRB or other relevant Ethic Committee and the Sponsor or the Sponsor’s designee within 3 months after termination or completion of the study.

10 Abbreviations and Terms

AE	Adverse Event
BGST	Brodsky Grading System for Tonsils
BMI	Body Mass Index
CE	Communauté Européenne
CRF	Case Report Form
CSA	Central Sleep Apnea
EC	Ethical Committee
ECM	Extracellular Matrix
EEG	Electroencephalogram
EU	European Union
FDA	Food and Drug Administration
FU	Follow-Up
HV	High Voltage
IRB	Institutional Review Board
IRE	Irreversible Electroporation
IRE System	ENTire Medical Ltd. IRE device
NTIRE	Non-Thermal Irreversible Electroporation
OSA	Obstructive Sleep Apnea
SAE	Serious Adverse Event
SDB	Sleep Disordered Breathing
Sponsor	ENTire Medical Ltd.
TAHSI	The Tonsil and Adenoid Health Status Instrument
Tx	Treatment
UARS	Upper Airway Resistance Syndrome
UI	User Interface
VAS	Visual Analogue Scale

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