A Prospective, Multicenter Study Comparing Healing After Treatment with the Sonendo GentleWave™ System as Compared to a Traditional Root Canal Therapy Literature Control

The SUPREME Study

Protocol Number: CS-06

Revision: B

Date 23 March 2015

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Study Sponsor

SONENDO INC.

26061 Merit Circle, Suite 101

Laguna Hills, California 92653

Phone: (949) 766-3636

Fax: (949) 305-5201

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I have read this protocol and I approve the design of this study.

_____

Printed Name of V.P., Regulatory/Clinical Affairs & Quality

_____ _____

Signature of V.P., Regulatory/Clinical Affairs & Quality Date (DD/MMM/YYYY)

INVESTIGATOR APPROVAL PAGE

Sonendo Sponsored Study

A Prospective, Multicenter Study Comparing Healing After Treatment with the Sonendo GentleWave™ System as Compared to a Traditional Root Canal Therapy Literature Control (SUPREME)

Clinical Protocol Number: CS-06, Revision B

Date: 23 March 2015

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the use of the device. I will ensure that the study is conducted in compliance with the protocol, Good Clinical Practices and all applicable regulatory requirements.

Printed Name of Investigator

Investigator's Signature

Date

PERSONNEL AND FACILITIES

STUDY SPONSOR:

SONENDO INC.

SARA TISH RODRIGUEZ, DIRECTOR OF CLINICAL AFFAIRS

26061 MERIT CIRCLE, SUITE 102

LAGUNA HILLS, CALIFORNIA 92653

PHONE: (949) 766-3636

FAX: (949) 305-5201

EMAIL: CLINICAL@SONENDO.COM

1.0 STUDY SYNOPSIS

Study Title	A Prospective, Multicenter Study Comparing Healing After Treatment with the Sonendo GentleWave™ System as Compared to a Traditional Root Canal Therapy Literature Control (SUPREME)
Study Short Title	The SUPREME Study
Purpose	The purpose of this study is to assess healing rates following root canal therapy with the Sonendo GentleWave System as compared to a literature control.
Objective	The objective of this study is to evaluate healing and post procedure pain following root canal therapy (RCT) of 1st and 2nd molars treated with the Sonendo GentleWave System and to compare it to data presented in a traditional RCT literature control.
Sites	Up to 8 clinical sites in the United States
Study Design	A prospective, non-significant risk device, literature controlled, study evaluating healing rates for the Sonendo GentleWave System in the treatment of 1st and 2nd molars indicated for root canal therapy. All patients will receive root canal therapy with the Sonendo GentleWave System. All patients will be followed for 24 months post procedure.
Study Population	Up to 120 subjects, aged 18 to 75 years, who have a 1st or 2nd molar tooth indicated for root canal therapy, will be enrolled in the study.
Study Duration	Duration of 24 months Study Visits: Screening, Baseline, Treatment (within 7 days of Baseline) and 6, 12, 18, and 24 months. Expected Enrollment Commencement: August 2014 Expected Enrollment Period: January 2016 Expected Study Completion: March 2018
Sample Size	86 subjects Roll-in patients: Up to 5 per site Lost- to Follow-up 20%: 18 Subjects Total: Up to 120 patients
Roll-In Subjects	Roll-in subjects, up to 5 per clinical site, will be included in the study. The Sponsor will determine the required number of Roll-In cases depending on the Investigator's experience with the Sonendo

	GentleWave System and training. Roll-in cases may not be included in the final data analysis.
Study Cohorts	There will be two cohorts within the study. The two cohorts are defined as follows: • All subjects meeting the Treatment Complete criteria • All subjects meeting the Treatment Incomplete criteria Only subjects in the Treatment Complete Cohort will be followed for 24 months according to the study visit schedule. Only subjects in the Treatment Complete cohort will be included in the primary effectiveness and safety endpoint analyses.
Treatment Complete	Treatment Complete is defined as any subject that received 100% of the Sonendo GentleWave Treatment (Treatment) over the course of no more than two visits.
Definition of Sonendo GentleWave System Treatment	The Sonendo GentleWave System Treatment is defined as beginning when LuxaBite® (DMG) or a Sonendo Tooth Cap is placed until 100% completion of the Sonendo GentleWave System. All other procedures will be categorized as traditional RCT procedures.
Indication	The Sonendo GentleWave System is intended to prepare, clean, and irrigate 1st and 2nd molar teeth indicated for root canal therapy.
Primary Effectiveness Endpoint	Subject teeth in the Treatment Complete cohort that are healed or are healing at the twenty-four month follow-up visit. Healed is defined by absence of a radiographic indication of apical periodontitis (PAI <3) and absence of clinical signs and symptoms. Healing is defined by a reduction of radiolucency (if radiolucency is present at Baseline) and/or reduction of clinical signs and symptoms (if clinical signs and symptoms are present at Baseline) Secondary analysis will be completed after all Treatment Complete subjects complete the 12 month follow-up. Additional analysis may occur.
Primary Safety Endpoint	Incidence of device related adverse events as defined by perforation, instrument separation, root fracture, sodium hypochlorite accident, or Gutta Percha extrusion, as related to the device for the Treatment Complete cohort.

Secondary Endpoint(s)	The following outcomes will be assessed: 1. McGill Short Form Pain Questionnaire 2. Gracely Descriptor Differential Scale (DDS) 3. Patient Satisfaction Survey 4. AAE Case Difficulty Assessment 5. Soft Tissue Lesions 6. Swelling 7. Root Canal Therapy Retreatment 8. Treatment Time 9. Procedure Time 10. Periapical Index (PAI) analyzed utilizing radiographic analysis by independent reviewer 11. Cone Beam Computed Tomography (CBCT) Sub-Set Evaluation 12. Additional Radiographic Analysis may be completed
Pre-Procedure Inclusion Criteria	1. The patient is 18 to 75 years of age 2. The subject tooth is indicated for root canal therapy 3. The subject tooth is a 1st or 2nd molar 4. The patient is mentally and physically able and willing to fully comply with this protocol, including adhering to the follow-up schedule and completing forms and questionnaires 5. Signed Informed Consent Form
Pre-Procedure Exclusion Criteria	1. Poor oral hygiene according to a Poor, Fair, Good Scale Poor: There is evidence of: generalized inflammation and swelling of gingival tissue, generalized bleeding on probing and/or generalized plaque/calculus accumulation 2. Subject tooth with ≥ Class II Mobility 3. Subject tooth with Periodontal Pocket Depth ≥ 6 4. Periodontal probe reaches the apex of the subject tooth 5. Furcation involvement originating from periodontal disease, on the subject tooth, one or two adjacent teeth in direct contact with the subject tooth

	6. Subject tooth with ≥ Class III endodontic furcation involvement 7. Subject tooth with open or incompletely formed root apices 8. Vertical fracture, horizontal fracture, or perforation extending below the Cemento-Enamel Junction (CEJ) of the subject tooth 9. Caries or another condition of the subject tooth that a. prevents adequate seal of the device b. requires a separate procedure for crown lengthening c. requires a post d. provides inadequate biological width for crown retention 10. Any dental treatment on the subject tooth completed with the known use of devitalizers or formocresol 11. Subject tooth having previous or attempted pulpectomy or root canal therapy 12. One or two adjacent teeth in direct contact with the subject tooth requiring root canal therapy, pulpectomy or pulpotomy 13. Any tooth on the same side of the oral cavity as the subject tooth with a source of pain 14. Extraoral swelling on or around the subject tooth that has not undergone antibiotic treatment or a procedure to treat the swelling prior to RCT 15. Any condition that would preclude tolerance of a root canal therapy including but not limited to being in a reclined and prolonged position in a dental chair, use of a dental dam, or ability to have an open mouth for extended periods of time (>15 minutes) (e.g. history of seizure within the last 5 years, severe asthma, or extreme gag reflex) 16. Any other condition that the Investigator determines is unacceptable for enrollment into the study 17. Nonodontogenic facial pain 18. History of cancer within the oro-maxillofacial region 19. History of any cancer within the last two years, including skin cancer 20. History of head and/or neck radiation therapy

	21. Immunocompromised patients (i.e. corticosteroid usage) 22. Any medical history that affects blood coagulation (e.g. bleeding disorders) 23. Long-term or current usage of medication that affects blood coagulation. This includes herbal or other over the counter medications. Exception: Patients taking daily low dose Aspirin (81mg) or patients that can stop Aspirin or Ibuprofen products three (3) days prior to procedure, should not be excluded from the study. 24. Patients with any medical condition causing chronic pain (e.g. spinal injury) 25. Patients on long-term (i.e. more than three months) narcotic, opioid, or other similar analgesic (e.g. daily narcotic pain medication for spinal disease) 26. Any infectious diseases (e.g. HIV, Hepatitis B, Hepatitis C, Tuberculosis, BCE, or Prion diseases) 27. Uncontrolled diabetes or diabetics with unknown hemoglobin A1c levels 28. A known allergy to local anesthetics, titanium carbon-nitride or stainless steel 29. A pacemaker, implantable cardiac defibrillator (ICD), or other implanted electronic medical device 30. Patient is institutionalized, a prisoner, homeless, or on active military duty 31. Patients with documented current alcohol and/or drug abuse 32. Patient is pregnant or planning to become pregnant within the duration of the study 33. Participated in any clinical study in the past 30 days
Intra-Procedure Inclusion Criteria	1. Successful removal of caries on the subject tooth 2. Successful completion of build-up to restore the subject tooth crown when used in combination with the Occlusal Plate. *Exception*: This does not apply when the Tooth Cap is utilized.
Intra-Procedure Exclusion Criteria	1. Use of laser devices 2. Subject tooth that requires crown lengthening

	3. Subject tooth that requires a post 4. Subject tooth that provides inadequate biological width for crown retention 5. Perforation of the subject tooth 6. Vertical fracture or horizontal fracture below the Cemento-Enamel Junction (CEJ) of the subject tooth 7. Internal or external root resorption that affects the use of Sonendo GentleWave System
Assessments Completed for the Study	Data will be collected on the following Standard of Care Assessments: • Medical and Dental History and Exam • Medication Regime • Periapical Radiographs: PA Parallel Periapical Index (PAI) Scoring by an independent reviewer • General Dental Assessments including Tooth Number, Oral Hygiene, Probing Pocket Depth, Mobility Assessment, Swelling, Soft Tissue Lesions and Furcation Involvement • Endodontic Assessments including Periradicular Tests (Percussion and Palpation), Cold Test, Root Resorption, Pulp Diagnosis, and Periradicular Diagnosis • Procedural details including Calcification Assessment, Irrigation, and Material Utilization • Sonendo GentleWave System Devices Utilized • Traditional Root Canal Therapy Devices and Instruments Utilized • Procedure Time (dental dam placement to removal) • Sonendo GentleWave Treatment Time (Treatment Time) • Cone Beam Computed Tomography (CBCT) Sub-Set Evaluation • Radiographic Evaluation of Obturation • Adverse Events
Questionnaires Completed for the Study	The following questionnaires will be completed for the study: • McGill Short Form Pain Questionnaire at Baseline, 1, 2, 3, 7 and 14 days post-procedure, at all Follow-up Visits and at Unscheduled Visits, as necessary

	• Gracely Descriptor Differential Scale (DDS) at Baseline, immediately post procedure and 1 day post procedure • Patient Satisfaction Survey immediately post procedure • AAE Case Difficulty Assessment post procedure

2.0 INTRODUCTION AND RATIONALE

2.1 General Background

Over 15 million cases of root canal therapy (RCT) are performed each year in the United States[1]. If performed effectively, RCT can be the best treatment for a necrotic or irreversibly inflamed pulp. However, the current methodologies rely on technologies invented over 200 years ago and which are not only inefficient, but also are associated with several procedural and safety issues, such as leaving uninstrumented recesses, root weakening, ledge formation, perforations, over-instrumentation, instrument separation, extrusion of debris into the periapical tissue, and periapical extrusion of sodium hypochlorite. The introduction of the Sonendo GentleWave device may substantially reduce and, in some cases, eliminate the risks associated with a traditional root canal procedure.

2.2 Drawbacks of Current Methods in Root Canal Therapy

After more than two centuries, modern endodontics still suffers from a number of procedural and safety issues that diminish the achievement of consistently successful outcomes in RCT. Some of these issues are briefly discussed below.

2.2.1 Leaving Uninstrumented Recesses

The conventional method of RCT does not uniformly and completely clean canals. Although metallic files (e.g nickel titanium) are flexible and conform to the curvature of a canal, they still do not touch all root canal surfaces as they are fundamentally rigid, round pieces of metal. Therefore, it is typical for at least 35% (and as high as 50%) of the canal surface to be passed over during instrumentation[2, 3]. This bypass, combined with the inefficiency of current irrigation methods, results in 40% to 60% of canals still yielding positive cultures after instrumentation and irrigation with different sodium hypochlorite (NaOCl) concentrations[4, 5].

Another factor increasing the chance of leaving uninstrumented recesses is the canal curvature. This issue is specifically the case for long and narrow oval canals (ratio of major/minor canal diameters is greater than 2.0). Hulsmann et al.[6] studied the RCTs performed on mandibular molars using two different rotary instruments. They found that 81-88% of the canals will be left with some degree of uninstrumented recesses. Vaudt et al.[7] compared the performance of the Alpha System and ProTaper Universal with manual techniques and found that in 80% of the manually treated curved mesial canals of mandibular molars more than 25% of the canal surface remained uninstrumented.

2.2.2 Root Weakening

Instrumentation increases the diameter of the root canals to allow for proper flow of irrigant and obturation. This filing also removes dentin from canal walls, which weakens the root[8]. From a strength and materials perspective, it is straightforward that removing the natural dentinal structure reduces the tooth strength. Consequently, RCT may be associated with some level of root weakening. A high price is paid solely due to the inability of the current methodology to remove the pulp and the bacteria without damaging and weakening the natural structure of the

tooth. This adverse treatment effect becomes even more pronounced when the canal cross-sectional shape deviates from a circular shape and when canals are curved. For instance, long oval shapes are generally impossible to completely instrument without perforating or severely weakening the roots[9]. While nature is elegant, it rarely forms perfectly straight and wide canals that are well-situated to the equipment and technical limitations of the current standard of care.

2.2.3 Ledge Formation

Ledge formation is among the most commonly observed procedural errors during root canal instrumentation[10]. It is defined as a deviation from the original canal curvature, where communication with the apical constriction is lost. The presence of a ledge might exclude the possibility of achieving an adequately shaped canal that reaches the ideal working length, which may result in incomplete instrumentation and disinfection of the root canal system, as well as incomplete filling of the canal. The root canal space apical to the ledge is difficult to adequately clean and shape; therefore, ledges frequently result in persistent periapical pathosis after the endodontic treatment. Consequently, there is a causal relationship between ledge formation and unfavorable endodontic treatment outcomes[11, 12, 13, 14, 15, 16]. Some of the reported frequencies of ledge formation include: 11% by Bergenholtz et al.[17], 10% by Stadler et al.[18], 46% by Greene and Krell[15], 52% by Kapalas and Lambrianidis[12], and 25% by Eleftheriadis and Lambrianidis[19]. In one study[12], endodontists performed RCTs and reportedly created ledges in 33% of previously untreated canals and 41% of endodontic retreatment cases.

2.2.4 Perforation

Root perforations are shown to be one of the eminent causes of endodontic failures[20]. They are artificial openings in root walls created by boring, piercing, or filing that result in a communication between the pulp space and periodontal tissues[21]. These openings may cause secondary periodontal involvement and eventual loss of the tooth[22]. Iatrogenic perforations are often due to insufficient attention to the details of internal anatomy and a failure to consider anatomic variations. They may also be due to lack of information on the canal anatomy and morphology, as the dental radiographs only provide a buccolingual view of the tooth. Accidental root perforations, which may have serious implications, occur in approximately 2–12% of endodontically treated teeth[20, 21, 22, 23]. Bacterial infection emanating either from the root canal or the periodontal tissues, or both, prevents healing and promotes inflammatory sequels where the supporting tissues have been exposed. This bacterial exposure may be followed by painful conditions, abscesses, and fistulae, including bone resorption processes. Once an infectious process has established itself at the perforation site, prognosis for treatment is precarious and the complication may prompt extraction of the affected tooth[23].

2.2.5 Penetration of Instruments into the Periapical Tissue

Another commonly occurring iatrogenic error is the penetration of the endodontic instruments beyond the apical foramen, which results in damage to the periapical tissue and triggers foreign body immunological response (Figure 1). It is well accepted and proven that instrumentation beyond the apical foramen should be avoided as it reduces the success rate[24, 25, 26, 27]. In clinical

practice, one of the major difficulties is that the apical constriction cannot be detected radiographically[29]. According to ElAyouti et al.[28], the endodontic instruments penetrate beyond the apical foramen in 25% of cases. In 10% of cases, the file penetration is greater than 1mm. They argued that this penetration is mainly due to the fact that the apical foramen is located laterally in 78% to 93% of the cases. ElAyouti et al.[28] determined that a seemingly accurate working length (ending radiographically 0 to 2mm short of the radiographic apex) frequently resulted in instrumentation beyond the apical foramen. Even the advent of apex locators has not been able to resolve the issue as the function of apex locators is consistent in only 85% of patients[29].

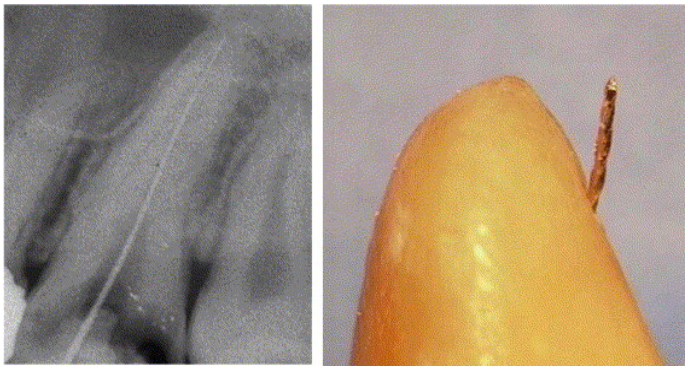

Figure 1: The photograph of the extracted tooth illustrates the file beyond the apical foramen. Examiners indicated that the file was at the correct radiographic working length. This penetration error is an example of an underestimation of the actual working length distance, causing the file to be too long[30].

2.2.6 Instrument Separation

After decades of research and development, intracanal breakage of root canal instruments continually causes endodontists and patients considerable anxiety. Removal of separated instruments requires additional dentin removal and irrigation which generally results in perforated or severely weakened roots. An 18-month study involving 7,159 discarded rotary NiTi instruments from 14 endodontists worldwide reported a frequency of 5% instrument separation[31]. A review of the literature reveals that the mean prevalence of retained fractured endodontic hand instruments (mostly stainless steel files) is approximately 1.6%, with a range of 0.7% to 7.4%[32]. However, it bears mentioning that much of the published literature is comprised of outcome studies that do not specifically evaluate prevalence of instrument fracture. The mean clinical fracture frequency of rotary NiTi instruments is approximately 1.0% with a range of 0.4 to 3.7%[32]. Suter et al.[33] analyzed the probability of removing fractured instruments from root canals. During an 18-month study, they found that a fractured instrument was left inside 1% of all the root canals treated.

2.2.7 Extrusion of Debris into the Periapical Tissue

During preparation, irrigant (i.e. sodium hypochlorite) and debris (e.g. bacteria, dentin debris, and necrotic tissue) are often extruded into the periradicular region, leading to periapical inflammation and postoperative flare-ups[34]. It is known that inflammatory reactions can cause

bone resorption, edema, and pain[35]. All preparation techniques and instruments have been reported to be associated with extrusion of infected debris, even when preparation is maintained short of the apical terminus[36, 37, 38, 39, 40, 41, 42, 43, 44]. There are several studies analyzing the apical debris extrusion resulting from different instrument types and instrumentation techniques[38, 39, 45, 46]. Various conclusions have been drawn, but all studies agree that, regardless of the instrument type or the technique, currently practiced RCT is associated with some level of apical debris extrusion, which affects the healing process significantly.

2.2.8 Extrusion of Sodium Hypochlorite into the Periodontal Tissues

Root canal irrigation with sodium hypochlorite (NaOCl) plays an important role in the debridement and disinfection of the root canal system and is an integral part of traditional root canal procedures. However, sodium hypochlorite has a pH of approximately 11 to 12, causing injury upon entering the body. If the irrigating solution permeates the periodontal tissues, it can result in inflammation, postoperative pain, and extended healing. Other commonly reported responses include severe pain, a rapidly developing edema, hematomas, necrosis, and abscesses. Several reports of the effects of sodium hypochlorite accidentally spreading beyond the interior regions of the tooth can be found in the literature[47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57]. Additionally, instrumentation and the enlargement of canals have a significant effect on the penetration of sodium hypochlorite through the apical foramen. Salzgeber and Brilliant[46] showed that instrumentation beyond a size 35 may allow penetration of irrigant beyond the apex and into periapical tissue.

2.3 Healing Rates for Traditional Root Canal Therapy

While the literature presents many different definitions of healing, any future endodontic clinical studies should utilize a healing endpoint based upon both clinical and radiographic findings. The radiographic finding should be based upon the periapical index score, with PAI 1 or 2 indicating success. Additionally, no clinical signs or symptoms should be present. Separating complete healing and incomplete healing will also more clearly present study results.

Success rates over time varied widely across the literature. Generally, most healing had occurred 1 year following root canal treatment, though healing was shown to take up to 4 years or more. Thus, success rates should also be presented at each time-point studied and not just a cumulative number over a range of follow-up periods. An approximate success rate for 1 year follow-up would be 68-70% while that success rate would increase to 80-85% after four years.

While effective chemomechanical canal preparation is extremely important, the literature indicated other factors significantly affected long-term prognosis for the patient. If a patient presented with apical periodontitis and had a periapical lesion, the long-term success was significantly lower. Thus, including a large number of patients with a pre-operative periapical radiolucency could result in lower long-term success rates. Effective obturation to within 2 mm within the radiographic apex and effective coronal restorations also improved long-term success. The number of roots treated and mid-treatment complications could also impact success rates. These facts highlight the importance of choosing the appropriate patient

population and standardizing the treatment regimen in clinical studies so that the variable being studied can be reliably assessed.

While a number of studies have been published regarding the healing and success rates following root canal treatment, the quality of this literature is generally less than other medical disciplines. A dearth of randomized, controlled trials exists in endodontic research, and a large number of retrospective studies are published. Finally, the lack of standardization of study design and clinical endpoints across studies makes the comparison of results between studies difficult at best. *(See Appendix I. Healing Literature Report)*

2.4 Sonendo GentleWave Technology Overview

The Sonendo GentleWave System (System) introduces a novel method of cleaning root canals that may be safer, less invasive, and more efficient. It has been designed to conserve more of the natural structure of the tooth and to minimize procedural and safety issues. The System, when used in combination with the Molar Handpiece (Figure 2), has been designed to clean root canals of molar teeth without requiring excessive enlargement of root canals. Traditional root canal therapy devices enter into the root canal of the tooth, whereas the System's treatment tube (guide tube) is designed to enter only to the pulpal chamber. It has been designed to clean the root canals remotely and simultaneously in a matter of minutes.

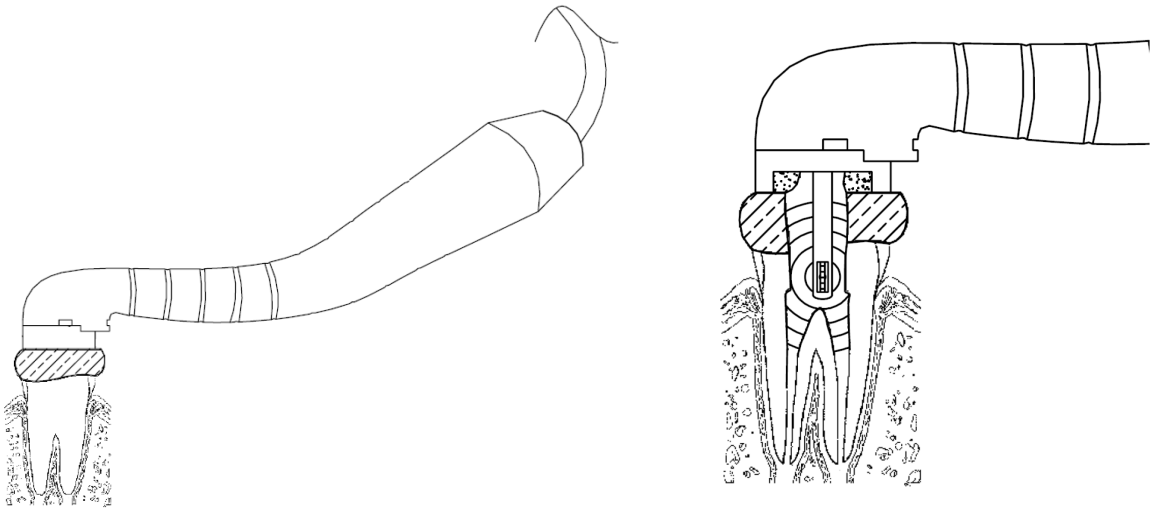

Figure 2: Illustrations of the Molar Handpiece applied to a molar tooth. The Handpiece delivers a stream of treatment fluid in such a way as to generate a set of physicochemical phenomena that effectively, yet safely, clean the pulpal space of the tooth.

The Sonendo GentleWave treatment is designed for use with minimal instrumentation of the root canals in order to facilitate obturation of the root canal system. It is also thought that by minimizing the shaping process, a large amount of tooth structure may be saved, as opposed to traditional practice, which typically removes this structure. In addition, the System may reduce the risks associated with instrumentation, i.e. ledge formation, instrument separation, and perforation. Unlike conventional root canal treatment, irrigation solutions are delivered into the root canal system without requiring the irrigation component (i.e. the needle) to be inserted inside each individual canal. With the System, the solution enters the tooth at about 1 mm above

the pulpal chamber floor. This alteration from traditional root canal therapy may minimize the risk of irrigant extrusion into the periapical tissues.

2.5 Device Description

The Sonendo GentleWave System (System) is comprised of two units: the Sonendo GentleWave™ Console (Console) and the Molar Handpiece (Handpiece). The Console prepares and delivers treatment fluid to the Handpiece. The Handpiece comes with additional accessories needed to interface the Handpiece to the Console and tooth.

The System delivers treatment fluid into the axis cavity of the tooth in such a way that it creates hydroacoustic waves within the treatment fluid accumulated inside the tooth. The treatment fluid delivered into the tooth removes organic tissues and smear layer from the root canal system. The Console aspirates the treatment fluid and organic/inorganic matter from the tooth into the Console waste canister. The Console is designed for use with a treatment fluid of 8-10% sodium hypochlorite (NaOCl) without surfactants, 17% neutral pH buffered ethylenediaminetetraacetic acid (EDTA), and distilled water.

All of the materials coming into contact with the patient and/or the treatment fluid have known biocompatibility and a history of acceptable use in medical device applications.

2.5.1 Console

The Console (Figure 3) is a semi-stationary unit designed to prepare and deliver treatment fluid to the Handpiece. It is comprised of a treatment fluid Delivery Hose, a Suction Hose, a Purge Port, Evacuation Tubing, a User Interface Screen, a distilled water Reservoir, an NaOCl Reservoir, an EDTA Reservoir, a Waste Canister, and a Foot Pedal. Similar to the dental handpieces currently used in dentistry, the System is activated by a foot pedal, which must remain depressed in order to operate the System.

The Console is made up of five functional subgroups of components:

1. Delivery System

   The Delivery System is composed primarily of a pump. This pump operates in two cycles: a delivery cycle and a retraction cycle. During the delivery cycle, the piston moves forward in order to pump the treatment fluid through the outlet. The pump operates with two cylinders/pistons (continuous flow). During the retraction cycle, more water is drawn into the cylinder, readying the System for the upcoming cycle.

2. Mixing System

   The Mixing System is designed to mix and prepare the treatment fluids NaOCl, water and EDTA at the prescribed concentrations.

3. Degassing System

   The Degassing System is configured to reduce dissolved gasses from treatment fluids as they are passed through the degassing cartridge.

4. User Interface

   A touch-panel screen is mounted on the outside of the Console and provides the operator with real-time feedback relating to the treatment progress.

5. Evacuation System

   The Evacuation System is designed to prevent waste and treatment fluid from spraying or spilling from the Handpiece or tooth during normal operation. In addition, the fluid that passes through the System and into the Handpiece is then returned to the Console through the Evacuation System.

Figure 3. Example image of the Sonendo GentleWave System

The treatment fluid containers are connected to the System using standard quick-connects that are included in Food and Drug Administration's (FDA) U.S. Pharmacopeia (USP) Class VI list of established materials. The System is designed to comply with applicable electrical safety standards for medical electrical equipment. The user will activate and maintain operation of the System by depressing the foot pedal.

2.5.2 Molar Handpiece

The Molar Handpiece comes with the following accessory items which are needed, in addition to items commonly used in standard dental practice, in order to successfully carry out the Sonendo GentleWave treatment:

1. Molar Handpiece

   The Handpiece consists of a quick-connect fitting to the delivery hose, fluid conduit, distal fluid chamber, nozzle, delivery tube, and clamshell plastic grip.

The Handpiece is designed to be a single use, disposable component. The Handpiece may be sterilized by a steam autoclave or gamma irradiation.

The Handpiece, containing proprietary features such as a nozzle and a treatment tube (also called a guide tube), delivers a stream of treatment fluid into the pulp chamber of the tooth. This is completed in such a way that it creates hydroacoustic waves within the treatment fluid accumulated inside the tooth. The treatment fluid is a low concentration sodium hypochlorite (NaOCl) solution, which is the most commonly used irrigant in traditional endodontic procedures for dissolution of organic matter and for added sterility. The stream of solution delivered into the tooth is designed to be dispersed and deflected by proprietary features at the distal end of the treatment tube. This is designed to create a safe yet effective circulation (irrigation) of the solution within the tooth. These physicochemical phenomena occurring inside the pulpal space may be powerful enough to remove all of the organic tissues and microorganisms from the root canals in just a few minutes, yet gentle enough not to affect the hard structure of the tooth or the periodontal tissues enclosing the roots. The used treatment fluid flows from the tooth into a Waste Canister rendering the procedure dry and contained.

The Handpieces are produced by approved suppliers based on Sonendo drawings and are inspected upon receipt. They are checked for dimensional accuracy, performance, production, and inclusion of appropriate material certifications in the shipment documentation.

2. Single Use Suction Hose

   The single use Suction Hose is designed to suction air and fluids during the procedure. The Suction Hose is made from Tigon tubing and Policarbonate fittings.

3. Occlusal Plate

   The Occlusal Plate features a handle, a circular area, and a pin protruding from the middle of the circular area. This pin helps locate the center of the tooth surface in order to facilitate locating the pulp chamber. The Occlusal Plate is used to form a flat surface, called an Occlusal Platform, so that the Handpiece can create a seal against it. The Occlusal Plate is made from polycarbonate.

4. Molar Tooth Caps

   The Molar Tooth Caps are designed to provide the interface, the Occlusal Platform that is required for use with the Molar Handpiece when a substantial amount of the tooth's original structure is missing. In these situations, it is difficult to prepare the tooth for treatment with the Sonendo GentleWave System using the Occlusal Plate and impression material, so the Molar Tooth

Caps may be used instead. The main components of the Molar Tooth Cap consist of polypropylene.

5. Set of Depth Gauges

   The Depth Gauges are utilized to determine the depth of the pulp chamber. This is done to ensure the correct selection of the Sealing Cap size and correct positioning of the Treatment Tube (guide tube) within the pulp chamber. The Depth Gauges are made from polycarbonate.

6. Set of Sealing Caps

   The Sealing Caps are designed to adapt the Molar Handpiece to different sized teeth. Each Sealing Cap is designed to properly position the Handpiece with respect to the floor of the pulp chamber. The Sealing Caps are made from polycarbonate, medical grade adhesives, silicone and/or polycarbonate.

2.5.3 Treatment Fluids

The three treatment fluids utilized during the System operation are sodium hypochlorite (NaOCl), ethylenediaminetetraacetic acid (EDTA) and distilled water. All fluids are introduced for treatment through the Console and Handpieces.

The first treatment fluid is a NaOCl solution. NaOCl is the most commonly utilized irrigation fluid during traditional root canal therapy, which is typically introduced via a dental syringe. This solution is prepared by the Console, which mixes distilled water and regular 8-10% NaOCl.

In addition, the root canals will be irrigated with EDTA solution. This solution is prepared by the Console, which mixes distilled water and 17% EDTA. The System automatically introduces EDTA into the tooth, while standard dental practice uses a dental syringe to release EDTA.

2.6 Sonendo System Technology: Previous Clinical Experience

Five clinical studies have used the Sonendo System Technology. The first two studies are closed. The CS-01 dose feasibility clinical study included twenty-nine (29) patients. The CS-02 system feasibility clinical study enrolled twenty (20) patients that were treated with the Sonendo System Technology prior to tooth extraction.

Three studies are currently enrolling patients. Clinical study CS-02.1 has enrolled twenty (20) patients that were treated with the Sonendo GentleWave System prior to tooth extraction. In the CS-03 PURE study, molar teeth treated with the Sonendo System are evaluated for long-term performance of the System. A total of hundred and twenty two (122) patients have been enrolled to date in this study.

A fifth clinical study is CS-05, which is a randomized extraction study that will compare cleaning results in teeth treated with Sonendo GentleWave System and in teeth treated with traditional RCT. A total of seven (7) patients have been enrolled to date in this study.

A total of 198 patients have been treated with the Sonendo System.

3.0 STUDY PURPOSE AND OBJECTIVES

The purpose of this study is to assess healing rates and post-procedure pain following root canal therapy with the Sonendo GentleWave System as compared to a literature control.

3.1 Primary Effectiveness Endpoints

Subject teeth in the Treatment Complete cohort that are healed or are healing at the twenty-four month Follow-up Visit.

Healed is defined by absence of a radiographic indication of apical periodontitis (PAI <3) and absence of clinical signs and symptoms.

Healing is defined by a reduction of radiolucency (if radiolucency is present at Baseline) and/or reduction of clinical signs and symptoms (if clinical signs and symptoms are present at Baseline)

Secondary analysis will be performed after all Treatment Complete subjects have completed the 12 month Follow-up Visit.

3.2 Primary Safety Endpoints

Incidence of device related adverse events as defined by perforation, instrument separation, root fracture, sodium hypochlorite accident, or Gutta Percha extrusion, as related to the device for the Treatment Complete cohort.

3.3 Secondary Endpoints

The following outcomes will be assessed:

1. McGill Short Form Pain Questionnaire[58]
2. Gracely Descriptor Differential Scale (DDS) [59]
3. Patient Satisfaction Survey
4. AAE Case Difficulty Assessment
5. Soft Tissue Lesions
6. Swelling
7. Root Canal Therapy Retreatment
8. Treatment Time
9. Procedure Time
10. Periapical Index (PAI) analyzed utilizing radiographic analysis by independent reviewer
11. Cone Beam Computed Tomography (CBCT) Sub-Set Evaluation
12. Additional Radiographic Analysis may be completed

4.0 STUDY DESIGN

A prospective, non-significant risk device, literature controlled, study evaluating healing rates for the Sonendo GentleWave System in the treatment of 1st and 2nd molars indicated for root canal therapy.

All patients will receive root canal therapy with the Sonendo GentleWave System. All patients will be followed for 24 months post procedure.

5.0 STUDY POPULATION

Up to 120 subjects, aged 18 to 75 years, who have a 1st or 2nd molar tooth indicated for root canal therapy, will be enrolled in the study.

5.1 Pre-Procedure Inclusion Criteria

1. The patient is 18 to 75 years of age
2. The subject tooth is indicated for root canal therapy
3. The subject tooth is a 1st or 2nd molar
4. The patient is mentally and physically able and willing to fully comply with this protocol, including adhering to the follow-up schedule and completing forms and questionnaires
5. Signed Informed Consent Form

5.2 Pre-Procedure Exclusion Criteria

1. Poor oral hygiene according to a Poor, Fair, Good Scale
2. Subject tooth with ≥ Class II Mobility
3. Subject tooth with Periodontal Pocket Depth ≥ 6
4. Periodontal probe reaches the apex of the subject tooth
5. Furcation involvement originating from periodontal disease, on the subject tooth, one and/or two adjacent teeth in direct contact with the subject tooth
6. Subject tooth with ≥ Class III endodontic furcation involvement
7. Subject tooth with open or incompletely formed root apices
8. Vertical fracture, horizontal fracture, or perforation extending below the Cemento-Enamel Junction (CEJ) of the subject tooth
9. Caries or another condition of the subject tooth that
    a. prevents adequate seal of the device
    b. requires a separate procedure for crown lengthening
    c. requires a post

d. provides inadequate biological width for crown retention

10. Any dental treatment on the subject tooth completed with the known use of devitalizers or formocresol
11. Subject tooth having previous or attempted pulpectomy or root canal therapy
12. One or two adjacent teeth in direct contact with the subject tooth requiring root canal therapy, pulpectomy or pulpotomy
13. Any tooth on the same side of the oral cavity as the subject tooth with a source of pain
14. Extraoral swelling on or around the subject tooth that has not undergone antibiotic treatment or a procedure to treat the swelling prior to RCT
15. Any condition that would preclude tolerance of a root canal therapy including but not limited to being in a reclined and prolonged position in a dental chair, use of a dental dam, or ability to have an open mouth for extended periods of time (>15 minutes) (e.g. history of seizure within the last 5 years, severe asthma, or extreme gag reflex)
16. Any other condition that the Investigator determines is unacceptable for enrollment into the study
17. Nonodontogenic facial pain
18. History of cancer within the oro-maxillofacial region
19. History of any cancer within the last two years, including skin cancer
20. History of head and/or neck radiation therapy
21. Immunocompromised patients (i.e. corticosteroid usage)
22. Any medical history that affects blood coagulation (e.g. bleeding disorders)
23. Long-term or current usage of medication that affects blood coagulation. This includes herbal or other over the counter medications. Exception: Patients taking daily low dose Aspirin (81mg) or patients that can stop Aspirin or Ibuprofen products three (3) days prior to procedure, should not be excluded from the study.
24. Patients with any medical condition causing chronic pain (e.g. spinal injury)
25. Patients on long-term (i.e. more than three months) narcotic, opioid, or other similar analgesic (e.g. daily narcotic pain medication for spinal disease)
26. Any infectious diseases (e.g. HIV, Hepatitis B, Hepatitis C, Tuberculosis, BCE, or Prion diseases)
27. Uncontrolled diabetes or diabetics with unknown hemoglobin A1c levels
28. A known allergy to local anesthetics, titanium carbon-nitride or stainless steel

29. A pacemaker, implantable cardiac defibrillator (ICD), or other implanted electronic medical device
30. Patient is institutionalized, a prisoner, homeless, or on active military duty
31. Patients with documented current alcohol and/or drug abuse
32. Patient is pregnant or planning to become pregnant within the duration of the study
33. Participated in any clinical study in the past 30 days

5.3 Intra-Procedure Inclusion Criteria

1. Successful removal of caries on the subject tooth
2. Successful completion of build-up to restore the subject tooth crown when used in combination with the Occlusal Plate.
   Exception: This does not apply when the Tooth Cap is utilized.

5.4 Intra-Procedure Exclusion Criteria

1. Use of laser devices
2. Subject tooth that requires crown lengthening
3. Subject tooth that requires a post
4. Subject tooth that provides inadequate biological width for crown retention
5. Perforation of the subject tooth
6. Vertical fracture or horizontal fracture below the Cemento-Enamel Junction (CEJ) of the subject tooth
7. Internal or external root resorption that affects the use of Sonendo GentleWave System

6.0 DENTAL CONE BEAM CT SUB-SET

Dental cone beam computed tomography (CBCT) systems are a variation of traditional cone beam systems. The CBCT systems used by dental professionals rotate around the patient, capturing data using a cone-shaped X-ray beam. These data are used to reconstruct three-dimensional (3D) images of the patient's dental anatomy (teeth)[60].

Subjects enrolled in the study may be included in a CBCT subset. All subjects that have access to the clinical sites with CBCT scanners may be included in the subset.

7.0 STUDY PROCEDURES

7.1 Pre-Screening Visit by Screening Dentist

Pre-Screening Visits can be conducted by a Screening Dentist (SD). Screening Dentists are general dental practitioners that normally refer patients for endodontic treatment to an endodontist. For the purpose of the study, Screening Dentists are the dentists who are part of

the study and are trained on the screening aspect of the study. Patients that appear to be eligible will be initially contacted through the Screening Dentist's own patient pool.

A patient will visit the Screening Dentist, according to standard of care, to be evaluated for root canal therapy.

The Screening Dentist will, according to standard of care, use a Screening Protocol and Screening Form (*see Appendix III. Screening Protocol*) to evaluate:

1. The patient's medical and dental health
2. The patient's eligibility as a study candidate

In addition, the GP or the SD should have completed the following:

1. Caries removal on the subject tooth and restoration, if applicable.
2. If caries are present underneath a crown, inlay or onlay then removal of the crown, inlay or onlay should occur in addition to caries removal and resin based restorative material restoration.
3. Caries removal on any tooth on the same side of the oral cavity as the subject tooth.
4. Extraction of partially erupted, malposed, carious, impacted wisdom tooth; and/or extraction of retained roots that may affect the outcome of root canal therapy on the subject tooth.
5. Treatment of any tooth on the same side of the oral cavity that has a source of pain.
6. Dental cleaning (full mouth) if not completed within six (6) months of Pre-Screening. In the case of patients who have heavy calculus and plaque accumulation tendencies, a full mouth dental cleaning should be completed even if the last dental cleaning was performed within six (6) months of Pre-Screening.

These above mentioned items should have been completed, as necessary, prior to screening the patient for the study according to standard of care dental procedures.

These screening candidates will be responsible for any standard of care costs associated with any of the above treatments or visits.

No Protected Health Information (PHI) will be collected on the Screening Form. The patient will be identified by a screening code on the Screening Form (*see Section 7.1.1 Screening Code)*.

If the patient is successfully pre-screened, the SD will send the following to the Sponsor:

- One (1) Periapical (PA) digital and/or hard copy redacted radiograph taken within two (2) months of Pre-Screening.
- One (1) Bitewing (BW) digital and/or hard copy redacted radiograph taken within two (2) months of Pre-Screening.
- PA radiograph has to show the periradicular tissue surrounding the subject tooth roots.

- BW radiograph has to show interproximal aspects of the coronal portion of the subject tooth, teeth adjacent to the subject tooth, and the opposing teeth in that quadrant.
- Redacted camera images of the patient's smile using retractors and the occlusal surface of the subject tooth are requested. If camera images are not available, then full mouth radiographs are requested for screening.
- Completed and signed Screening Form.

In addition, the SD should send the following to the PI's clinical site designee:

- The last dental visit notes for the patient. At a minimum, this should include information on the patient's dental treatment on the subject tooth and any assessments performed at the screening visit.
- Contact information for the patient. At a minimum, this includes phone number, address, and email, if applicable.
- Any other pertinent information required for treatment.

For a particular patient the SD may submit all eligible teeth for review. This Pre-Screening submission will include separate Screening Forms, as well as pertinent radiographs and camera images for all eligible subject teeth.

The Sponsor will not accept incomplete or inaccurate submissions and will not process study payments until required items are received and verified.

Both Screening Dentists and PIs conduct a medical and dental review and assessments on a patient. The Screening Dentist performs this review only as part the pre-screening process. Information collected by a Screening Dentist will not be included as study data (i.e. Screening Form, pre-screening radiographs, and dental notes). Only information collected by a PI will be used as study data. The data collected or assessments performed by a PI supersede those completed by a Screening Dentist. Source data verification will occur using the subject's dental file.

7.1.1 Screening Code

The patient will be identified by a screening code. The Sponsor will generate a Screening Code for each subject tooth that is sent in for a patient on the Screening Form. (If more than one subject tooth is submitted for the same patient, each tooth will receive a unique screening code.) The screening code should be six (6) alphanumeric characters: FML-XXX. The first set of three (3) characters (FML) is the initials of the PI or Screening Dentist. If there is no middle initial, a dash will be used. The second set of three (3) characters (XXX) is a sequential number starting at 001; each screening site will start at 001. Therefore, the first patient screened by a PI or Screening Dentist with the initials ABC will have the screening code ABC-001.

7.2 Pre-Screening Review and Notification

7.2.1 Pre-Screening by the PI

For patients pre-screened and approved by a PI, the PI will send the Screening Information to the Sponsor along with any required radiographs and camera images. The PI or a clinical site designee will schedule the patient for a Baseline Visit if the Screening Visit and Baseline Visit are not on the same day.

7.2.2 Pre-Screening by the Screening Dentist

For patients pre-screened by a Screening Dentist, the Sponsor will review the information provided to ensure completeness and eligibility, and, if eligible, will then forward the completed documentation to a PI for review.

7.2.3 Notification of Pre-Screening Outcome to the Screening Dentist

After the PI and the Sponsor determine patient eligibility for the study, the Screening Dentist will be notified. If the patient is eligible, the PI or clinical site designee will schedule the patient for a Baseline Visit at the clinical site; at this visit; the patient will complete the screening process for the study.

7.2.4 Pre-Screen Failures

If, during the Pre-Screening Process, the PI and/or the Sponsor determine that the patient is not eligible for the study, the patient will be considered a Pre-Screen Failure. Pre-Screen Failures will be treated and followed according to standard of care by their Screening Dentist or Endodontist, but will not be documented or followed for study purposes.

7.3 Prior to Baseline Visit

Patients who have a tooth approved for inclusion in the study and have had sinusitis or symptoms of sinusitis within the last 3 months may be required to receive a CBCT scan prior to the Baseline Visit**.** If the patient is included into the study, this CBCT may be used for the Baseline CBCT scan.

7.4 Baseline Visit

7.4.1 Informed Consent

Once the patient arrives for the Baseline Visit, the informed consent process may begin. The PI or clinical site designee will review the Informed Consent Form (ICF) with the patient *(see Appendix II. Informed Consent).* The patient will be given the opportunity to ask questions and will be allowed sufficient time to consider the information provided. The PI will confirm the patient's understanding and consent for the study. Written consent will be obtained, which will occur prior to any data collection for the study.

In addition, the patient is informed within the ICF of possible attendance by the Sponsor and/or Sponsor representative during the Procedure Visit.

The ICF will be signed and dated by the PI, patient and clinical site designee executing the consent process. The patient shall be given a copy of the signed ICF.

7.4.1.1 Consent for Audio-Video Recordings and Photographs Release

In addition to the ICF, all patients will be provided with an Audio-Video Recording and Photograph Release Form. If the patient agrees and signs the ICF, the Sponsor will be able to obtain audio-video recordings and/or photographs of the patient's oral cavity and root canal treatment performed during the patient's participation in the study. The patient's participation in the study is not contingent upon agreeing to this consent.

7.4.2 Cone Beam Computed Tomography (CBCT) Consent

All patients will be provided with information regarding dental CBCT scanning for the study. If the patient agrees, they may be included in a study subset where dental CBCT scans will be obtained for the study.

7.4.3 Screening

After the ICF has been signed, additional screening may occur to determine if the patient meets the inclusion and none of the exclusion criteria. The patient will undergo standard of care endodontic and dental assessments necessary to determine the patient's eligibility according to the Pre-Procedure Inclusion and Exclusion Criteria.

7.4.4 Baseline Exam

The PI will perform the following standard of care assessments and evaluations prior to the procedure, if they were not already completed:

1. Medical and Dental History and Exam
    a. Medical History: Only those histories related to endocrine/metabolic, hematologic, musculoskeletal, and immunological will be collected for the study.
2. Medication Regime: Only prescribed herbal or over the counter systemic antibiotics, analgesics, and anti-inflammatory medications taken during the duration of the study (24 months post procedure) and the prior three months will be documented for this study.
    - Any antibiotics, analgesics or anti-inflammatory medications provided intra-procedure by the PI during the Baseline and Procedure Visits will be collected for the study and will be documented on the Concomitant Medication Log.
    - Any antibiotics, analgesics and anti-inflammatory medications should be collected if prescribed or provided post Procedure Visit, and at all Follow-ups.
3. McGill Short Form Pain Questionnaire: The McGill Pain Questionnaire (MPQ) is one of the most widely used tests for the measurement of pain. It provides information on sensory, affective, and evaluative dimensions of pain experience and is capable of discriminating among different pain problems.

4. Gracely Descriptor Differential Scale (DDS): This scale is an intensity and unpleasantness scale. The scale includes both verbal and numeric characteristics.

5. Diagnostic Radiographic Analysis: Periapical (PA) Parallel Radiograph, showing the periapical region surrounding the subject tooth should be collected for each visit. Additional radiographs completed as necessary by the PI will be collected for the study.

6. Periapical Index (PAI) Score[61] analyzed by independent reviewer
   Up to three (3) independent reviewers will be provided radiographs in order to complete the PAI scoring. Independent reviewers will be blinded to the site, subject, and visit when completing the PAI score. This is being done to eliminate bias.
   - Score of 1: Normal
   - Score of 2: Small changes in bone structure
   - Score of 3: Changes in bone structure with some mineral loss (bone loss)
   - Score of 4: Periodontitis with well-defined radiolucent area (apical periodontitis)
   - Score of 5: Severe Periodontitis with exacerbating features (apical periodontitis)

   Note: A Protocol Deviation CRF will not be completed if PAI score was not completed by an independent reviewer for a particular visit. In addition there is no defined study window for completion of PAI scoring by an independent reviewer.

7. Dental Cone Beam Computed Tomography (CBCT) X-rays, as applicable

8. Intra-Oral Examination including, but not limited to:
   a. Tooth Number: Based on the Universal Tooth Numbering System (1-32)
   b. Oral Hygiene: Oral hygiene should be graded on a score of Poor, Fair, or Good.
      - Poor:
        There is evidence of: generalized inflammation and swelling of gingival tissue, generalized bleeding on probing and/or generalized plaque/ calculus accumulation
      - Fair:
        There is evidence of: localized mild to moderate inflammation of the gingival tissue, mild localized swelling of the gingival tissue, localized plaque/calculus accumulation and/or localized bleeding on probing
      - Good:
        There is evidence of: healthy gums and Minimal plaque. No evidence of gingival inflammation and no bleeding on probing.
   c. Subject Tooth Assessments including:

i. Probing Pocket Depth[62]: The distance between the height of the free gingival margin and the height of attachment apparatuses below (bone, cementum, and periodontal ligament). Using a calibrated periodontal probe, the periodontal pocket depth should be recorded on the mesial, middle, and distal aspects of both the buccal and lingual sides of the tooth

ii. Mobility[63]

- None: No distinguishable sign of movement.
- Class I: The first distinguishable sign of movement greater than normal.
- Class II: Horizontal tooth movement no greater than 1 mm.
- Class III: Horizontal tooth movement greater than 1 mm, with or without the visualization of rotation or vertical depressability.
- Any mobility other than none should be considered abnormal.

iii. Swelling: This assessment includes the type and location of swelling.

iv. Soft Tissue Lesions: This assessment includes the lesion presence, color and size where applicable. This assessment shall also include ulcerations and fistula/sinus tract.

v. Cold Test[63]

- Normal: A sensation is felt, but disappears immediately upon removal of the stimulus
- Negative: Lack of response to stimulus
- Lingering: Lingering or intensification of a painful sensation after the stimulus is removed
- Immediate: Excruciating, painful sensation as soon as the stimulus is placed on the tooth
- Delayed: A painful sensation is felt after an initial delay

vi. Root Resorption

vii. Furcation Involvement/Furcation Defect[64, 65]

- Class I: The furcation can be probed, but not to a significant depth.
- Class II: The furcation can be entered into but cannot be probed completely through to the opposite side.
- Class III: The furcation can be probed completely through and through.
- Class IV: The furcation can be probed through and through, and recession reveals a visible furcation.

9. Endodontic Assessments including:

a. Pulp Diagnosis[66]:

- Normal Pulp: A clinical diagnostic category in which the pulp is symptom-free and normally responsible to pulp testing.
- Reversible Pulpitis: A clinical diagnosis based on subjective and objective findings indicating that the inflammation should resolve and the pulp return to normal.
- Symptomatic Irreversible Pulpitis: A clinical diagnosis based on subjective and objective findings indicating that the vital inflamed pulp is incapable of healing. Additional descriptors: lingering thermal pain, spontaneous pain, referred pain.
- Asymptomatic Irreversible Pulpitis: A clinical diagnosis based on subjective and objective findings indicating that the vital inflamed pulp is incapable of healing. Additional descriptors: no clinical symptoms but inflammation produced by caries, caries excavation, trauma.
- Pulp Necrosis: A clinical diagnostic category indicating death of the dental pulp. The pulp is usually nonresponsive to pulp testing.

b. Periradicular Tests[63] (Percussion and Palpation):

- None (-): No discomfort at all.
- Mild (+): Little discomfort, but may be noticeable by the patient.
- Moderate (++): Some noticeable discomfort.
- Severe (+++): Definitive discomfort.

c. Periradicular Diagnosis:[66]

- Normal Apical Tissue: Teeth with normal periradicular tissues that are not sensitive to percussion or palpation testing. The lamina dura surrounding the root is intact, and the periodontal ligament space is uniform.
- Symptomatic Apical Periodontitis: Inflammation, usually of the apical periodontium, producing clinical symptoms including a painful response to biting and/or percussion or palpation. It might or might not be associated with an apical radiolucent area.
- Asymptomatic Apical Periodontitis: Inflammation and destruction of apical periodontium that is of pulpal origin, appears as an apical radiolucent area, and does not produce clinical symptoms.
- Acute Apical Abscess: An inflammatory reaction to pulpal infection and necrosis characterized by rapid onset, spontaneous pain, tenderness of the tooth to pressure, pus formation, and swelling of associated tissues.
- Chronic Apical Abscess: An inflammatory reaction to pulpal infection and necrosis characterized by gradual onset, little or no discomfort, and the intermittent discharge of pus through an associated sinus tract.

- Condensing Osteitis: Diffuse radiopaque lesion representing a localized bony reaction to a low-grade inflammatory stimulus, usually seen at apex of tooth.

After assessments are completed, the patient may be prescribed medication(s) for pain management according to standard of care procedures. If analgesic medications need to be provided to the patient in order to complete one or more of the assessments, the assessments that require a pain response (i.e. cold test, percussion and palpation) should be completed prior to providing these medications.

Upon determining that the patient meets all the Pre-Procedure Inclusion and none of the Pre-Procedure Exclusion Criteria, the patient may proceed to the Procedure Visit.

If the patient does not meet all of the Pre-Procedure Inclusion and/or meets any of the Pre-Procedure Exclusion Criteria, the patient will be considered a Screen Failure (see *Section 7.6.1 Screen Failures).*

All redacted source documentation with PI signature should be provided to the Sponsor for filing after each study visit. If changes are made to the source documents after PI signature, the updated source documents should be provided to the Sponsor for filing.

Both Screening Dentists and PIs conduct a medical and dental review and assessments on a patient. The Screening Dentist performs this review only as part the pre-screening process. Information collected by a Screening Dentist will not be included as study data (i.e. Screening Form, pre-screening radiographs, and dental notes). Only information collected by a PI will be used as study data. The data collected or assessments performed by a PI supersede those completed by a Screening Dentist. Source data verification will occur using the subject's dental file.

7.4.5 Baseline Exam Re-Assessment

For most patients, the Baseline and Procedure Visits will be on the same day. The patient and/or PI may choose to have the Procedure Visit occur on a day separate than that of the Baseline Visit.

If the Procedure Visit is not on the same day as the Baseline Visit, the Procedure must occur within seven (7) days. If the Procedure Visit is not completed within seven (7) days of the Baseline Visit, the Baseline Exam results are no longer valid and must therefore be repeated and captured on a new source document. Only data captured on the final Baseline Visit will be used for data analysis and will be monitored. All assessments listed under *Section 7.4.4 Baseline Exam* need to be repeated if the Procedure Visit is not completed within seven (7) days of the Baseline Visit.

7.5 Procedure Visit

7.5.1 Sonendo GentleWave System Preparation

Prior to use of the Sonendo GentleWave System, the System and auxiliary equipment need to be prepared for treatment. Follow the Manufacturer's Operator's Manual and IFU for set-up of the System.

After the Sonendo GentleWave System is prepared, prepare for root canal therapy.

7.5.2 Root Canal Therapy Procedure Preparation

During RCT preparation, the PI should assess the subject tooth to determine if the tooth meets all of the Intra-Procedure Inclusion and none of the Intra-Procedure Exclusion Criteria. The RCT preparation is to be performed using standard endodontic practices.

1. Use of a dental bib is recommended.
2. Protective safety eyewear is required.
3. Anesthetize the subject tooth and surrounding area.

   Note: If at any stage throughout RCT preparation, the subject expresses pain, sensitivity or discomfort, the PI may provide more anesthetic per standard practice.
4. Isolate the subject tooth by placing a rubber dam.
5. If using an Occlusal Plate, it is recommended to clamp the distal adjacent tooth, if a distal adjacent tooth is present. If using a Tooth Cap, it is recommended to clamp the subject tooth.
6. Use of a putty or caulking (i.e. OraSeal® (Ultradent) or equivalent) along the subject tooth and rubber dam interface for optimum isolation of the subject tooth is recommended.
7. The subject tooth may be disinfected (e.g. using chlorhexidine or betadine).
8. Any caries and/or dental fillings (e.g. amalgam) on the subject tooth must be removed. If a crown, inlay or onlay is present, it does not require removal unless necessary for treatment or if caries and/or leakage are present below the crown, inlay or onlay.

   Note: If there is tissue present that may affect caries removal and/or crown restoration, sear off the tissue according to standard dental practice.
9. Use of caries detector to ensure that all caries are removed even if caries are not visibly present or cannot be detected with a dental probe is recommended.

   Note: Ensure that the tooth is restorable without a post and has adequate biological width for restoration after caries removal. If not, the patient will be considered a Screen Failure (see Section 7.6.1 Screen Failures).

10. When necessary, restore/build-up the missing subject tooth structure with permanent restorative and bonding materials. Ensure the permanent restorative material is fully cured prior to treatment with the GentleWave System.

    Note: If there are any caries left, they will be removed by the Sonendo GentleWave System, and this can cause leakage. This leakage will require any build-up material to be removed and replaced. If a crown, inlay or onlay comes off prior to or during treatment, it is recommend that the entire tooth structure be re-built or the crown or inlay or onlay be re-cemented unless an adequate seal can be created.

11. Prepare a conservative endodontic access opening defined as a straight line path from the coronal orifice to the full working length per standard endodontic procedure. If a crown, inlay or onlay is present, the access opening may be performed through it as long as a caries detector is used post access.

    Note: Make sure the endodontic access is performed properly (per standard practice, i.e. pulp horns are removed and there is sufficient exposure of the pulpal cavity and floor).

7.5.3 Orifice Negotiation

Orifice negotiation for the study is defined as locating, accessing, finding or negotiating through the orifice of each canal.

1. Locate the orifices of each canal of the subject tooth.
    a. Ultra-sonic and sonic devices may be used for removal of calcification and/or orifices negotiation.
    b. Use of lasers is not permitted for the study.

Note: Use of orifice openers or Gates Glidden are allowed for tortuous or heavily calcified canals.

Note: If laser devices are used the patient will be considered a Screen Failure as this meets Intra-Procedure Exclusion for the study.

7.5.4 Minimal Shaping

1. Prior to starting the minimal instrumentation process, it is recommended to utilize PA radiographs or cone beam to estimate the length of each root.
2. A syringe of ≥ 0.5% NaOCl along with lubrication during the minimal shaping process is required according to standard of care.
3. Gain patency. Use of a 6, 8, or 10 hand file to gain patency along with an apex locator is required per standard of care. Patency for use with the Sonendo GentleWave System is defined as 0.5mm from the apical foramen.
4. Use of an endodontic ruler to ensure no apical penetration throughout the instrumentation process is required per standard of care.

Note: There should be no apical penetration of any subject teeth. If apical penetration occurs on an upper subject tooth, the patient will be considered as a Screen Fail (see Section 7.6.1 Screen Failures).

5. Removal of calcification is recommended. Ultra-sonic and sonic devices may be used for removal of calcification

   Radiographic verification of the working length for each canal using a Gutta Percha or size 10 or 15 file is recommended.

   Note: There should be no apical penetration of any subject teeth. If apical penetration occurs on an upper subject tooth, the patient will be considered as a Screen Fail (see Section 7.6.1 Screen Failures).

6. Minimal shaping the canals to a maximum hand files size 25.02 is required.

   Note: There should be no apical penetration of any subject teeth. If apical penetration occurs on an upper subject tooth, the patient will be considered as a Screen Fail (see Section 7.6.1 Screen Failures).

7. Minimal shaping of all canals using rotary file size to a maximum of 25.08 is required. The Master Apical File (MAF) is defined for the study as the final apical file.

   Note: There should be no apical penetration of any subject teeth. If apical penetration occurs on an upper subject tooth, the patient will be considered as a Screen Fail (see Section 7.6.1 Screen Failures).

8. Continue with Sonendo GentleWave System preparation (*see Section 7.7 Sonendo GentleWave System Treatment).*

7.6 Enrollment

Patients are considered to be enrolled after all Pre- and Intra-Procedure Inclusion Criteria and none of the Pre- and Intra-Procedure Exclusion Criteria are met and beginning of Luxabite material or Tooth Cap. Once patients are enrolled in the study, they are considered subjects.

7.6.1 Screen Failures

Patients that were consented but that did not meet all Pre- and Intra-Procedure Inclusion Criteria and/or met any Pre- and Intra-Procedure Exclusion Criteria are considered Screen Failures. Screen Failures will be treated and followed according to standard of care by their Screening Dentist or endodontist, but will not be documented or followed for study purposes.

A Screen Failure patient will be counseled by the endodontist on any treatment they require. The patient will be responsible for any standard of care treatments.

7.6.2 Subject Identification

Once a subject is enrolled in the study, they will be assigned a Subject Identification (ID) code. A Subject ID is a numeric six (6) digit code: XXX-XXX. The first set of three (3) numbers is the clinical site number. The second set of three (3) numbers is a sequential number starting at 001; each

clinical site will start at 001. Therefore, the first subject enrolled at site 101 is 101-001, the second is 101-002, and so forth.

If the subject is a Roll-In subject (as defined in *Section 19.1 Roll-In Subjects*), then the second three (3) digit code begins with an R to designate the subject as a Roll-In. The R is followed by a sequential two digit number for that site. Therefore, the first Roll-In subject enrolled at site 101 is 101-R01, the second is 101-R02, and so forth.

7.7 Sonendo GentleWave System Treatment

After a subject has been enrolled in the study, the PI will begin the Sonendo GentleWave System treatment.

The Sonendo GentleWave System Treatment is defined as beginning when LuxaBite or a Tooth Cap is placed (start of placement) until 100% completion of the Sonendo GentleWave System. All other procedures will be categorized as traditional RCT procedures.

7.7.1 Sonendo GentleWave System Treatment Process

Use the Manufacturer's Operator's Manual and IFU for the treatment process.

To ensure optimal performance of the Sonendo GentleWave System, please ensure that the following has occurred prior to start of the Sonendo GentleWave System:

- Ensure that the occlusal platform is placed and formed correctly.
- Ensure that the cotton pellet is removed from the pulp chamber.
- Utlize Depth Gauge to size Sealing Cap for pulp chamber.
- If Sealing Cap size is incorrect, change the size. It is recommended to choose the next smaller Depth Gauge (larger Sealing Cap).
- Ensure that the guide tube is placed in the center of the pulp chamber.

If the sealing cap and/or handpiece must be changed during the treatment, a new handpiece should be obtained. Once the new handpiece has been attached according to the IFU, the treatment should recommence where it was stopped and treatment should continue.

7.7.2 Leakage

If fluid or air leaks in and/or out of the Sealing Cap and/or the subject tooth, stop the Sonendo GentleWave treatment and determine the cause. Leakage may be caused by:

- Presence of caries
- Fracture
- Break in the build-up or leakage from LuxaBite or Tooth Cap

  Note: There are certain circumstances that will require build-up to be removed and then replaced in order to perform a successful treatment after a leak
- Hand position of the PI
- Other items such as an issue with the irrigants

To avoid leakage, the following precautions should be taken:

- Do not tilt rock, rotate or move the handpiece.
- If the PI needs to adjust their hand or position, or if the patient wants to move, the treatment should be paused prior to movement.

Once a leak has been corrected, restart the Sonendo GentleWave System treatment. Treatment will commence from the point where it was stopped (exception: during leak test).

7.8 Control of Bleeding

Bleeding and control of bleeding during any RCT is expected and is considered standard of care. Bleeding is typically controlled through a combination of paper point usage, waiting for the bleeding to stop, starting the cone fit process and usage of intra-canal medications. If bleeding cannot be controlled and prevents the System from treating the tooth, the PI should pack the tooth with calcium hydroxide ($Ca(OH)_2$) and restore the tooth with temporary material until the patient can be scheduled for a Second Procedure Visit according to standard of care.

7.9 Second Procedure Visit

The Sonendo GentleWave treatment may be completed on a subsequent visit, a Second Procedure Visit. The Second Procedure Visit can be scheduled according to standard of care.

At this visit, the PI should remove the $Ca(OH)_2$ with the Sonendo GentleWave System. Use of files or irrigation to remove $Ca(OH)_2$ is not allowed for the study.

7.10 Inability to Complete Treatment

If, for any reason, Sonendo GentleWave treatment cannot be completed over the course of no more than two visits, the subject will be considered as a Treatment Incomplete Subject. Subjects in the Treatment Incomplete Cohort will be documented as such but will not be followed for the study. No additional data will be collected on the Treatment Incomplete Cohort. Reasons for incomplete treatment may include, but are not limited to, periodontal issues, uncontrolled bleeding, root fracture, patient reported pain, etc.

These subjects will be counseled by the PI on any treatment they require. Subjects in the Treatment Incomplete Cohort will be responsible for any standard of care treatment.

7.11 Obturation

After the Sonendo GentleWave System treatment is completed; obturation, and coronal seal are required according to standard endodontic practices.

1. Dry the pulp chamber and the root canals in preparation for obturation.
2. Obturate the subject tooth using standard endodontic techniques. A warm vertical compaction method should be utilized as the obturation technique for this study.
3. A cone fit radiograph is recommended prior to completion of obturation.
4. Complete obturation to the full working length leaving the coronal 1-2mm for

extension of the restorative materials of each canal is recommended.

7.12 Coronal Seal

1. It is recommended to use a cotton ball dipped in alcohol to wipe the pulpal chamber floor and prepare for coronal seal and build-up.
2. Seal the pulp chamber floor and canal orifices with using a permanent restorative material (approx. 3mm thick), according to standard of care.
3. Complete the case according to standard endodontic procedure.

7.13 Intra-Procedure Assessments and Evaluations

The following information, among others, will be collected during traditional root canal therapy and the Sonendo GentleWave Treatment.

1. Procedure Time: Defined for this protocol as the time from dental dam placement until dental dam removal.
2. Procedural Details: Working Length, Master Apical File size, Irrigation, Calcification Assessment, additional therapies or procedures utilized and Material Utilization.
3. Enrollment Time: Study Enrollment time is equivalent to Sonendo GentleWave System Treatment Start Time.
4. Sonendo GentleWave Treatment Start Time: Defined for this protocol as starting when the LuxaBite or Tooth Cap is placed (start of placement) on the subject tooth.
5. Traditional Root Canal Therapy devices and instruments utilized.
6. Sonendo GentleWave System devices utilized.
7. Sonendo GentleWave Treatment End Time: Defined for this protocol as when the Sonendo GentleWave System user interface screen indicates 100% completion.
    a. If the subject is required to return for a Second Procedure Visit, then the Sonendo GentleWave Treatment End Time for the first visit is defined as the time when the Investigator determines the subject tooth needs to be packed with calcium hydroxide.
    b. Sonendo GentleWave Treatment End Time for the First visit: Defined for this protocol as the last time when Sonendo GentleWave Treatment is stopped.
8. Medications: Any antibiotics, analgesics and/or anti-inflammatory medications provided intra-procedure by the PI will be collected for the study and will be documented on the Concomitant Medication Log.
9. Radiographic Assessment: Working Length and Cone Fit radiographs, if applicable.
10. Adverse Events **(*SEE SECTION** 10.0 Adverse Event)*

7.14 Post Procedure Assessments and Evaluations

The following information will be collected post procedure;

1. Diagnostic Radiographic Analysis: Periapical (PA) Parallel Radiograph, showing the periapical region surrounding the subject tooth should be collected for each visit. Additional radiographs completed as necessary by the PI will be collected for the study.
2. Cone Beam Computed Tomography (CBCT) radiograph post procedure is recommended.
3. Radiographic Evaluation of Obturation[67]:
    a. The PI will evaluate the radiographs to determine the level of obturation.
        i. Short Fill: Sealer or obturation material <2mm above the apex.
        ii. Flush Fill: Sealer or obturation material within 2mm of the apex.
        iii. Overfill: Sealer or obturation material >2mm below the apex.
        iv. Presence and size of sealer puff
4. AAE Case Difficulty Assessment[68]: This form will be utilized by the PI after every Procedure Visit to assign a level of difficulty to a particular case.
5. Gracely Descriptor Differential Scale
6. Patient Satisfaction Survey: This is a questionnaire that asks the patient to rate their experience of the root canal procedure they had and compare it with their previous root canal procedure experience, if applicable. The questionnaire also asks the patient to indicate any sensations or pain felt during the procedure.

If the PI prescribes any antibiotics, analgesics and/or anti-inflammatory medications post procedure; these medications will be documented at subject's next study visit if the medications were taken by the subject. If the prescribed medications were not taken by the subject, the clinical site designee should make a note of this on the source document.

All subjects are instructed to contact the PI and/or clinical site designee in case of increased pain or discomfort after the procedure. If during the wait period between the Procedure Visit and next study visit, the subject has increased pain or discomfort, the PI will provide the subject with standard post-operative care and guidance.

All redacted source documentation with PI signature should be provided to the Sponsor for filing after each study visit. If changes are made to the source documents after PI signature, the updated source documents should be provided to the Sponsor for filing.

7.15 Out-Patient Questionnaires

7.15.1 McGill Short Form Pain Questionnaire

Subjects will be asked to complete a McGill Short Form Pain Questionnaire for their physical mouth and tooth pain at 1, 2, 3, 7 and 14 days post-procedure and at all Follow-up Visits . This

form should be completed and returned to the clinical site designee at the next study visit or using certified mail or using a pre-paid FedEx envelope.

If the subject is unable to complete one or more outpatient McGill Short Form Pain Questionnaire(s) then the clinical site designee may call the subject and complete the questionnaire(s) themselves based upon responses provided by the subject.

7.15.2 Gracely Descriptor Differential Scale (DDS)

Subjects will be asked to complete a Gracely Descriptor Differential Scale Questionnaire wherein they will be asked to rate the sensation felt in the tooth treated with Sonendo GentleWave System at 1 day post-procedure. This form should be completed and returned to the clinical site designee at the next study visit or using certified mail or using a pre-paid FedEx envelope.

If the subject is unable to complete the outpatient Gracely Descriptor Differential Scale Questionnaire then the clinical site designee may call the subject and complete the questionnaire themselves based upon responses provided by the subject.

7.16 Crown Placement

Subjects enrolled in the study should obtain a permanent crown per standard of care. It is recommended that crown placement should occur within six weeks of the root canal therapy procedure per standard of care. For the protocol, final crown placement date will be the date CRC obtains from the subject and/or GP and/or the Investigator.

Pain and tenderness to percussion, palpation, ill-fitting margins, open margins, high occlusal contact points with the opposing teeth or any other restoration related issues after crown placement experienced by the patient or reported by the PI and/or SD and/or Crown Placement dentist, will not be considered an adverse event but will be documented.

7.17 Follow-Up Study Visits

The study follow-up visits will occur 6, 12, 18, and 24 months post-procedure. In addition, subjects may be requested to attend Follow-up Visits once a year after the twenty-four month follow-up for up to ten years.

7.17.1 Follow-Up Study Visit Windows

The visit windows are as follows:

- Treatment: Within seven (+7) days of the baseline visit
- 6 Month Visit: Plus or minus fourteen (±14) days.
- 12 Month Visit: Plus or minus thirty (±30) days
- 18 Month Visit: Plus or minus thirty (±30) days
- 24 Month Visit: Plus or minus forty-five (±45) days

7.17.2 Follow-Up Visit Evaluations and Assessments

These study follow-up visits will occur at the clinical site and the following assessments will occur according to standard of care at each visit:

1. Medication Regime: Only prescribed herbal or over the counter systemic antibiotics, analgesics, and anti-inflammatory medications taken during the duration of the study (24 months post procedure) and the prior three months will be documented for this study.

2. McGill Short Form Pain Questionnaire: The McGill Pain Questionnaire (MPQ) is one of the most widely used tests for the measurement of pain. It provides information on sensory, affective, and evaluative dimensions of pain experience and is capable of discriminating among different pain problems.

3. Diagnostic Radiographic Analysis: Periapical (PA) Parallel Radiograph, showing the periapical region surrounding the subject tooth should be collected for each visit. Additional radiographs completed as necessary by the PI will be collected for the study.

4. Periapical Index (PAI) Score analyzed by independent reviewer

   Up to three (3) independent reviews will be provided radiographs in order to complete the PAI scoring. Independent reviewers will be blinded to the site, subject, and visit when completing the PAI score. This is being done to eliminate bias.

   - Score of 1: Normal
   - Score of 2: Small changes in bone structure
   - Score of 3: Changes in bone structure with some mineral loss (bone loss)
   - Score of 4: Periodontitis with well-defined radiolucent area (apical periodontitis)
   - Score of 5: Severe Periodontitis with exacerbating features (apical periodontitis)

   Note: A Protocol Deviation CRF will not be completed if PAI score was not completed by independent reviewer for a particular visit. In addition there is no defined study window for completion of PAI scoring by independent reviewer.

5. Dental Cone Beam Computed Tomography (CBCT) at 12 and 24 months and additional as required by the PI.

6. Intra-Oral Examination including, but not limited to:

   a. Tooth Number: Based on the Universal Tooth Numbering System (1-32)

   b. Subject Tooth Assessments including:

      i. Probing Pocket Depth: The distance between the height of the free gingival margin and the height of attachment apparatuses below (bone, cementum, and periodontal ligament). Using a calibrated periodontal probe, the periodontal pocket depth should be recorded on the mesial, middle, and distal aspects of both the buccal and lingual sides of the tooth

      ii. Mobility

- None: No distinguishable sign of movement.
- Class I: The first distinguishable sign of movement greater than normal.
- Class II: Horizontal tooth movement no greater than 1 mm.
- Class III: Horizontal tooth movement greater than 1 mm, with or without the visualization of rotation or vertical depressability.
- Any mobility other than none should be considered abnormal.

iii. Swelling: This assessment includes the type and location of swelling.

iv. Soft Tissue Lesions: This assessment includes the lesion presence, color and size where applicable. This assessment shall also include ulcerations and fistula/sinus tract.

v. Root Resorption

vi. Furcation Involvement/Furcation Defect

- Class I: The furcation can be probed, but not to a significant depth.
- Class II: The furcation can be entered into but cannot be probed completely through to the opposite side.
- Class III: The furcation can be probed completely through and through.
- Class IV: The furcation can be probed through and through, and recession reveals a visible furcation.

7. Endodontic Assessments including:

a. Periradicular Tests (Percussion and Palpation)

- None (-): No discomfort at all.
- Mild (+): Little discomfort, but may be noticeable by the patient.
- Moderate (++): Some noticeable discomfort.
- Severe (+++): Definitive discomfort.

b. Periradicular Diagnosis:

- Normal Apical Tissue: Teeth with normal periradicular tissues that are not sensitive to percussion or palpation testing. The lamina dura surrounding the root is intact, and the periodontal ligament space is uniform.
- Symptomatic Apical Periodontitis: Inflammation, usually of the apical periodontium, producing clinical symptoms including a painful response to biting and/or percussion or palpation. It might or might not be associated with an apical radiolucent area.
- Asymptomatic Apical Periodontitis: Inflammation and destruction of apical periodontium that is of pulpal origin, appears as an apical radiolucent area, and does not produce clinical symptoms.

- Acute Apical Abscess: An inflammatory reaction to pulpal infection and necrosis characterized by rapid onset, spontaneous pain, tenderness of the tooth to pressure, pus formation, and swelling of associated tissues.
- Chronic Apical Abscess: An inflammatory reaction to pulpal infection and necrosis characterized by gradual onset, little or no discomfort, and the intermittent discharge of pus through an associated sinus tract.
- Condensing Osteitis: Diffuse radiopaque lesion representing a localized bony reaction to a low-grade inflammatory stimulus, usually seen at apex of tooth

8. Adverse Events *(see Section 10.0 Adverse Event).*

After assessments are completed, the patient may be prescribed medication(s) for pain management according to standard of care procedures. If analgesic medications need to be provided to the patient in order to complete one or more of the assessments, the assessments that require a pain response (i.e. cold test, percussion and palpation) should be completed prior to providing this medication.

All redacted source documentation with PI signature should be provided to the Sponsor for filing after each study visit. If changes are made to the source documents after PI signature, the updated source documents should be provided to the Sponsor for filing.

In addition, the clinical site designee will report all significant findings at Follow-Up Visits to the Sponsor either via email or by sending redacted source documentation.

Subjects should be evaluated to determine if the subject tooth remains functional. If the subject tooth is or still requires healing, the subject should be evaluated closely. If the subject has clinical symptoms or signs after the twelve month follow-up, the PI should follow standard endodontic care, as applicable. All such care should be documented accordingly for the study.

7.18 Unscheduled Visits

Apart from the scheduled study visits, if the subject returns to the PI for a suspected adverse event (AE), the PI may perform tests and request additional information about what the subject is experiencing. Only those assessments that the PI deems as necessary for assessment of a possible AE will be collected. Assessments that are not completed during the Unscheduled Visit will not be considered as Protocol Deviations. The information collected at this visit will be recorded on appropriate Case Report Forms. An Unscheduled Visit will not be completed unless an AE is suspected.

All redacted source documentation with PI signature should be provided to the Sponsor for filing after each study visit. If changes are made to the source documents after PI signature, the updated source documents should be provided to the Sponsor for filing.

7.19 Mail, Telephone and Dentist Contact

If the subject is unable or unwilling to attend all study visits, the subject consents to be called or sent mail by the PI or clinical site designee to provide information about their dental status.

The data provided via telephone contact or mail may include the following:

1. Medical and Dental History and Exam
2. Medication Regime
3. McGill Short Form and/or Numeric Rating Scale

   The clinical site designee will follow the Numeric Rating Scale mentioned below or verbally ask questions on the McGill Short Form Pain Questionnaire. When asking the patient to rate their pain per the Numeric Rating Scale, the following question should be asked:

   "On a scale of 0 to 10, with 0 being 'no pain' and 10 being the 'most intense pain imaginable', what would you rate the severity of your tooth pain right now"?
4. Adverse Events

7.20 Subject Completion

Subjects are considered to have completed the study when they have completed the twenty-four (24) month follow-up examination. Subjects may be requested to have an in person or telephone follow-up visit every year after the twenty-four (24) month visit for up to ten (10) years.

8.0 SCHEDULE OF VISITS

Description	Screening	Baseline	Procedure[1] *(+7 ds)*	Post-Operative	1 day	2 days	3 days	7 days	14 days	6 mo. *(± 14ds)*	12 mo. *(± 30ds)*	18 mo. *(± 30ds)*	24 mo.[2] *(± 45ds)*	Unscheduled Visits
Screening Form by Screening Dentist or PI	X													
Images of Smile & Oclussal Surface	X													
X-Rays (Periapical)[3]	X	X	X	X						X	X	X	X	As needed
Medical and Dental History	X	X								X	X	X	X	As needed
Medication Regimen Review	X	X								X	X	X	X	As needed
Informed Consent		X								As needed	As needed	As needed	As needed	As needed
CBCT		X, if applicable		X, if applicable							X, if applicable		X, if applicable	As needed
McGill Short Form		X			X	X	X	X	X	X	X	X	X	As needed
Gracely DDS		X		X	X									
Periapical Index Score		X								X	X	X	X	As needed
General Dental and Endodontic Assessments		X								X	X	X	X	As needed
Sonendo GentleWave Treatment			X											
Root Canal Therapy			X											
Intra Assessments and Evaluations			X											
Post Operative Assessments and Evaluations				X										
Patient Satisfaction Survey				X										
AAE Case Difficulty Assessment				X										
Adverse Event Assessment			X	X						X	X	X	X	As needed

1. The procedure must be completed within seven days (7) of the baseline visit. For any treatment not completed within seven days of the baseline, the baseline assessments must be completed again within the time frame indicated. In addition, if a subject must return to the clinical site for completion of a procedure, as indicated in *Section 7.9 Second Procedure* Visit, this must also occur within seven days of the baseline.
2. Subjects may be asked to have a follow-up visit every year after the twenty-four (24) month visit for up to ten (10) years.
3. Only PA Parallel radiographs will be obtained.

9.0 PATIENT AND SUBJECT STATUS

9.1 Pre-Screen Failure

During the Pre-Screening Process, if the PI and/or the Sponsor determine that the patient is not eligible for the study, the patient will be considered a Pre-Screen Failure. Pre-Screen Failures will be treated and followed according to standard of care by their Screening Dentist or endodontist, but will not be documented or followed for study purposes.

9.2 Pre-Screen Closure

If a patient is eligible and approved for the screening process, but does not complete a Baseline Visit, the patient will be considered a Pre-Screen Closure. Patients that fall into this category may have been lost or missed a scheduled Baseline Visit. In order for a patient to be considered lost, the clinical site should attempt contact with the patient at least three times. The first two attempts may be by phone call and must be documented. The third attempt must be made via certified letter.

9.3 Screen Failure

Patients who were consented but did not meet all Pre-Procedure and Intra-Procedure Inclusion Criteria and/or met any Pre-Procedure or Intra-Procedure Exclusion Criteria are considered Screen Failures. Screen Failures will be documented as such for the study but will be followed according to standard of care. Screen Failures will not be followed for the study.

9.4 Subject versus Patient

Once a patient is enrolled in the study, they are considered a subject.

9.5 Enrolled

Eligible patients will be considered enrolled after all Pre-and Intra-Procedure Inclusion Criteria are met and none of the Pre- and Intra-Procedure Exclusion Criteria are met.

9.6 Treatment Complete and Treatment Incomplete

Treatment Complete is defined by any subject that received 100% of the Sonendo GentleWave Treatment (Treatment).

Subjects that do not meet the Treatment Complete definition above are considered Treatment Incomplete.

9.7 Termination

Subjects may be terminated from the study at the discretion of the PI for reasons related to the study treatment that would jeopardize a subject's health and/or welfare if they were to continue in the study. Terminated subjects may be replaced. Terminated subjects may not be included in final data analysis. Notification of a subject termination should be made immediately to the Sponsor.

9.8 Withdrawal

Subjects may be withdrawn from the study for non-treatment-related reasons only when no other option is possible. Reasons for withdrawal include, but are not necessarily limited to, voluntary withdrawal from the study by the subject.

The reason for withdrawal will be recorded on the appropriate Case Report Form. Withdrawn subjects may be replaced in the study. Notification of a subject withdrawal should be made immediately to the Sponsor.

9.9 Discontinuation

Subjects may be discontinued from the study for non-treatment-related reasons only when no other option is possible. Reasons for discontinuation include, but are not necessarily limited to, a subject that is unwilling or unable to cooperate with study requirements (medication regimen, follow-up visits, etc.). The reason for discontinuation will be recorded on the appropriate Case Report Form. Discontinued subjects may be replaced in the study. Notification of a subject discontinuation should be made immediately to the Sponsor.

9.10 Lost to Follow-up

A subject that is consented but does not attend the study required visits and/or does not respond to contact attempts will be considered lost to follow-up. The clinical site should attempt contact with the subject at least three times. The first two attempts may be by phone call and must be documented. The third attempt must be made via certified letter.

If the subject is unable or unwilling to come in for a study visit, the process for mail, telephone call or general dentist contact should be attempted and documented (*see Section 7.19 Mail, Telephone and Dentist Contact).* Lost to follow-up subjects may be replaced in the study.

10.0 ADVERSE EVENTS

10.1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject. An AE can therefore be any unfavorable and unintended sign or symptom, intercurrent illness, injury, or disease temporally associated with treatment whether or not related to the procedure or device.

- Mild: The AE is transient and easily tolerated by the subject.
- Moderate: The AE causes the subject discomfort and interrupts the subject's usual activities.
- Severe: The AE causes considerable interference with the subject's usual activities, may be incapacitating and may require hospitalization.

10.2 Definition of Serious Adverse Events (SAE)

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

- Results in death
- Is life-threatening (defined as any AE that places a person, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include an AE that, had it occurred in a more severe form, might have caused death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly or birth defect.

10.3 Adverse Event Assessments

Adverse Events (AEs) that occur during the Baseline, Treatment Visit(s) and all the other Follow-up Visits including the Unscheduled Visits will be assessed by PI, recorded in the patient's study chart and then transcribed onto the Adverse Event Form Case Report Form (CRF).

Pain, inflammation, swelling, or other reactions that are expected and associated with standard traditional root canal or dental procedures will not be considered adverse events for the study.

Those events that may be exacerbated intra-procedure or post-procedure will be considered adverse events if the PI determines that these expected reactions are exacerbated or different from those experienced with the standard traditional root canal or dental procedures.

AEs include, but are not limited to, the following:

- Observed or volunteered problems
- Complaints
- Physical signs and symptoms
- Medical condition which occurs during the study, having been absent at baseline
- Medical condition present at baseline, which appears to worsen during the study.

AEs related to only dental and endodontic procedures will be collected for the study.

In addition to recording the AE on the Adverse Event CRF, the PI should also prepare an AE narrative (a complete written summary of the event and its outcome). Each AE must be described as follows:

- Describe the event by stating the underlying cause (the diagnosis), coexisting disease, or other. In order to avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject's own words when

possible

- Note the duration by entering the date of onset, and date of resolution. If the event is present at the final study visit, the ongoing box must be marked
- Note the worst severity of the event as mild, moderate, or severe using the definitions provided in the protocol
- Note the outcome of the event
- Note the action taken as none, medical and/or surgical
- Note the relationship to surgical procedure and device
- Note any seriousness criteria

Any medication necessary for the treatment of an AE must be recorded on the Concomitant Medication CRF. If more than one distinct adverse event occurs, each event should be recorded separately.

In addition, PIs must report all AEs to their Institutional Review Board (IRB) and regulatory bodies according to applicable guidelines and regulations. A copy of the notification must also be submitted to the Sponsor.

10.4 Unresolved Adverse Events

Any subject terminated from the study due to an AE will be followed until the outcome of the event is determined.

Any subject that is discontinued, withdrawn, or lost to follow-up will have this information documented on the End of Study CRF. This is considered the End of Study for the patient and all unresolved AEs must be marked as ongoing on the AE or AE Resolution CRF.

All other AEs will be followed through to the end of the study. Any unresolved AE at the subject's final visit must be marked as ongoing on the AE CRF.

10.5 Assessment of Causality

Due to the temporal proximity of an AE to the procedure under investigation, there is a reasonable possibility that the procedure may have caused an AE or may have contributed to the severity or duration of an event caused by other means. Causality to the study procedure or device will be assessed by the PI and relationship will be classified in one of the following categories:

Definitely Not Related	Evidence exists that the adverse event definitely has a cause other than the procedure/device under investigation (e.g. pre-existing condition or underlying disease, intercurrent illness, or concomitant medication) and does not meet any other criteria listed.
Probably Not Related	An adverse event has little or no temporal relationship to the study device/study procedure and/or a more likely alternative etiology exists.
Possibly Related	A temporal relationship exists between the event onset and procedure under investigation, and appears with some degree of certainty to be related based on known therapeutic actions of the procedure/device under investigation. It cannot be readily explained by the patient's clinical state or concomitant therapies.
Probably Related	A temporal relationship exists between the event onset and procedure under investigation, and appears with some degree of certainty to be related based on known therapeutic actions of the procedure/device under investigation. It cannot be readily explained by the patient's clinical state or concomitant therapies.
Definitely Related	Strong evidence exists that the procedure/device under investigation caused the adverse event. There is a temporal relationship between the event onset and the procedure under investigation. There is strong therapeutic evidence that the event was caused by the procedure/device under investigation. The patient's clinical state and concomitant therapies have been ruled out as a cause.

10.5.1 Definition of Sonendo GentleWave System Treatment

The Sonendo GentleWave System Treatment is defined as beginning when LuxaBite or a Tooth Cap is placed until 100% completion of the Sonendo GentleWave System. All other procedures will be categorized as traditional RCT procedures.

10.6 Serious Adverse Event Reporting

PIs must report all Serious Adverse Events (SAEs) to the Sponsor within a timely manner of observing or learning of the event. For initial SAE reports, Investigators should record all case details that can be gathered within a timely manner on the SAE CRF and fax this information immediately upon completion to the Sponsor. The fax number is (949) 305-5201.

Each SAE must be followed with appropriate medical management until it's resolved or assessed as chronic or stable regardless of whether or not, in the opinion of the Investigator, the event is

thought to be related to the procedure. The Investigator will be required to provide complete information concerning each SAE to the sponsor within in a timely manner. This information must be recorded in the subject's medical record and then transcribed onto the Adverse Event CRF. The completed Serious Adverse Event Report (SAE) (including the Investigator's opinion of the relationship of the SAE to the procedure/device under investigation), copies of related results/reports, consultant report(s), and other relevant information will be faxed and/or mailed to the Sponsor.

All SAEs as described above, covering the period from a subject's enrollment in the study through seven (7) days following a subject's completion as per protocol or premature discontinuation from the trial will be managed and reported. The decision to report potential SAEs beyond the seven (7) day post-study period will be at the discretion of the Sponsor, unless otherwise advised by the IRB.

In addition, Investigators must report all SAEs to their Institutional Review Board (IRB) and regulatory bodies according to applicable guidelines and regulations. A copy of the notification must also be submitted to the Sponsor.

10.7 Unanticipated Adverse Device Effect

Pursuant to Part 812.3(s) of Title 21 of the Code of Federal Regulations, the definition of an Unanticipated Adverse Device Effect (UADE) means any serious adverse effect (as defined above) 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 clinical protocol 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.

Any UADE must be reported to the Sponsor either by telephone (949) 766-3636 or fax (949) 305-5201 within 24 hours of knowledge of that event. In addition, Investigators must report all UADEs to the IRB and regulatory bodies according to applicable guidelines and regulations.

The Sponsor will be responsible for informing Regulatory Authorities, all other IRBs, and Investigators participating in the study of the UADE according to the applicable guidelines and regulations.

10.8 Anticipated Adverse Events

10.8.1 Risks generally associated with any dental procedure include, but are not limited to, the following:

- Pain and/or discomfort
- Swelling or inflammation
- Pressure
- Numbness
- Paresthesia (tingling)
- Post-treatment infection

- Abscessed tooth
- Bleeding
- Tooth color changes
- Potential for re-treatment
- Reoccurring decay
- Reaction to medications or anesthesia
- Reaction to materials or chemicals used
- Sensitivity to hot and/or cold air pressure or sweets
- Breakdown of the inner filling causing infection and/or damage
- Weakening of the tooth
- Instrument breakage within the canal
- Perforating (creating a small hole) the side of the root
- Tissue damage
- Tooth crown fracture or breakage

10.8.2 Potential risks for <u>root canal therapy</u> include, but are not limited to, the following:

- Post-treatment pain and/or discomfort
- Post-treatment swelling or inflammation
- Pressure
- Numbness
- Paresthesia (tingling)
- Post-treatment infection
- Abscessed tooth
- Bleeding
- Tooth color changes
- Potential for re-treatment
- Reoccurring decay
- Reaction to medications or anesthesia
- Reaction to materials or chemicals used
- Extrusion of debris into the periapical tissue
- Sensitivity to hot and/or cold, air pressure or sweets
- Breakdown of the inner filling causing infection and/or damage
- Defective or inadequate restoration of the tooth which could lead to infection, leakage, loosening, detachment, or breakage
- Uninstrumented recesses of the tooth (i.e. missed canals or uncleaned areas)
- Instrument separation (i.e. breakage within the canal)
- Perforating (creating a small hole) the side of the root
- Damage to sinus floor or sinus infection
- Tissue damage
- Root weakening
- Ledge formation

- Weakening of the tooth
- Jaw bone infection or damage
- Worn out filling
- Broken or cracked filling
- Tooth root fracture or breakage
- Tooth crown fracture or breakage

10.9 Other Potential Risks

10.9.1 Radiation Risks

Radiation exposure will occur during radiograph examinations. Exposure to ionizing radiation while a low risk, has the potential to cause cancer and other risks.

There are also additional fetal risks associated with ionizing radiation exposure. Ionizing radiation is utilized in diagnostic procedures, such as radiographs, because without these procedures diagnostics on pulp diseases and other conditions would not occur.

10.9.2 Cone Beam Computed Tomography (CBCT) Radiation Risks

Although the radiation doses from dental CBCT exams are generally lower than other cone beam exams, dental CBCT exams typically deliver more radiation than conventional dental radiographic exams.

10.9.3 Pregnancy (risks for the fetus)

As dental procedures are associated with risks for pregnant women and the fetus, pregnant women will not be included in this research study. It will be recommended for subjects to avoid becoming pregnant during the study.

If a subject becomes pregnant during the duration of the study, the clinical site will document the pregnancy with a Memo to File. Study required radiographs or cone beam will not be collected for pregnant subjects but these subjects will still be followed for the duration of the study. The clinical site designee will not complete a Protocol deviation CRF for study required radiograph assessment not completed due to pregnancy. A Memo to File documenting this deviation will suffice.

10.10 Definitions of Adverse Events

Sodium Hypochlorite Accident is defined as follows: [69, 70]

Inadvertent extrusion of sodium hypochlorite past the protective apical constriction or through a lateral canal or root perforation which results in bleach injury as characterized by severe intermittent and/or constant pain, profuse bleeding combined with extraoral or facial swelling, edema, ecchymosis, and/or oral or facial parasthesia.

Extrusion of Filling Materials is defined as follows: [71, 72]

Gross overextension of the filling materials beyond the confines of the root canal and into the surrounding vital structures resulting in post operative discomfort, pain, parasthesia and/or anesthesia.

11.0 BENEFITS

The potential benefits of the Sonendo GentleWave treatment include the following:

- Significantly reduced pain
- Provide long-term pain relief
- Improved quality of life

These benefits are consistent with the effectiveness criteria studied in similar devices.

12.0 PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the PI or clinical site designee did not conduct the study according to the Clinical Protocol.

A clinical designee should notify the Sponsor of any protocol deviation(s), preferably via email. Deviations must be reported to the Sponsor regardless of whether medically justifiable, pre-approved by the Sponsor, or taken to protect the subject in an emergency. PIs must also adhere to procedures for reporting protocol deviations to the IRB in accordance with their specific IRB's reporting policies and procedures.

Regulations require that PIs maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol. For reporting purposes, the Sponsor classifies study deviations as major and minor:

- Major deviation: Any deviation from subject's Inclusion and Exclusion Criteria, subject's informed consent procedures or unauthorized device use. This also includes enrollment in another clinical study within 30 days of enrollment.
- Minor deviation: Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc.

It is untimely the PI's responsibility to determine the protocol deviation classification.

12.1.1 Protocol Deviation Types

The Sponsor has designated the following protocol deviation types for reporting purposes:

- Deviation from Informed Consent Process
- Patient did not meet Inclusion and/or met Exclusion Criteria
- Patient study visit out of study window
- Patient missed a study visit

- Assessment/Questionnaire was not completed
- Assessment/Questionnaire was completed out of study window
- Other

13.0 STATISTICAL METHODS

All required data for this study will be collected on paper or electronic Case Report Forms (CRFs). The Investigator (or designated study staff) will assure primary data collection based on source documented dental chart reviews. Independent monitoring will be performed to ensure that the investigator and his/her study team conducted the clinical investigation in accordance with contract specifications, study protocol, Declaration of Helsinki[73], and applicable local or national regulations, to ensure adequate protection of the rights and safety of subjects and the quality and integrity of the resulting data.

In general, quantitative variables will be summarized to indicate the population sample size (N), number of patients with available data (n), mean, standard deviation, median, minimum, and maximum values. Qualitative variables will be summarized by the population size (N), number of patients with available data (n), number of patients in each category, and the percentage of patients in each category. Analyses will be based on the Safety Population defined as all patients who receive the Sonendo GentleWave System procedure. Details of analysis methods will be described in the statistical analysis plan.

13.1 Sample Size

All patients will receive root canal therapy with the Sonendo GentleWave System and will be subsequently followed for 24 months post procedure. A sample size of 108 subjects, assuming a 20% lost to follow-up or Treatment Incomplete Cohort rate, will result in approximately 86 subjects who would be evaluable for the primary efficacy endpoint. A sample size of 86 evauable subjects provides approximately 90% power to detect a difference between a 85% response rate for subjects using the Sonendo GentleWave System against a null hypothesis of a 70% response rate based on data presented in literature for traditional root canal therapy, using a two-sided binomial test at the 5% level of significance.

13.2 Analysis Populations and Handling of Dropouts

The Safety Population is defined as all patients who receive the Sonendo GentleWave System procedure.

The Efficacy Evaluable population is defined as all subjects who enroll in the study and who receive 100% of the Sonendo GentleWave Treatment (Treatment Complete Cohort) over the course of no more than two visits. Analysis of efficacy data will be performed using the Efficacy Evaluable population. Efficacy analyses will be based on observed data only; no imputation methods will be used. Dropout subjects will not be replaced.

13.3 Demographics and Baseline Characteristics

Age, sex, height, weight medical history and other baseline characteristics will be collected at Screening. Continuous variables will be summarized using descriptive statistics; categorical variables will be summarized using counts and percentages.

13.4 Method for the Analysis of Primary Effectiveness Parameter

The primary effectiveness analysis will be based on Healing at twenty-four (24) months for Treatment Complete Cohort.

The proportion of subjects with healing, along with the exact 95% confidence interval, will be provided for healing at 24 months.

13.5 Secondary Analysis

Secondary analysis will be completed after all Treatment Complete subjects complete the 24 month follow-up.

13.6 Safety Analyses

Incidence of device related adverse events as defined by perforation, instrument separation, root fracture, sodium hypochlorite accident or Gutta Percha extrusion, as related to the device will be summarized for the Safety Population.

13.7 Handling Missing Effectiveness and Safety Data

Missing data will be reported as a protocol deviation. The data will be interpreted and noted as incomplete. The Sponsor has the discretion to disqualify a patient due to a protocol deviation.

For incomplete assessments or missing data, analysis will utilize the last observation carried forward method.

All data analyses will be conducted on data from subjects with the necessary observed endpoint data (complete case analysis).

13.8 Handling Post-Market Analysis

With the addition of Post Market enrollment subjects the sponsor may elect to provide separate subset analysis of pre and post market enrollment.

14.0 DATA REPORTING

A CRF casebook will be used for each subject enrolled in the study. All clinical data generated in the study will be reviewed for quality assurance review, data entry, and statistical analysis. All forms will be reviewed for completeness; evident recording errors will be rectified by contact with the appropriate clinical site.

The appropriate CRF will be completed by the PI or a clinical site designee after each visit. The PI will sign the CRFs to indicate verification and approval. All CRFs will be completed in a legible

manner in blue or black ink. Any corrections will be made by drawing a single line through the incorrect entry, entering the correct information, and initialing and dating the change.

If there is a discrepancy between a CRF and the source document and any significant data within the CRF is changed, the PI should re-sign the form to indicate verification and approval of the change(s).

If no Second Day Procedure, Protocol Deviation, AE, or AE Resolution occurred, then the associated CRF does not need to be completed or collected.

CRFs should be completed within two (2) weeks of a subject's study visit. The original signed forms, not copies, will be returned to the Sponsor.

All redacted source documentation with PI signature should be provided to the Sponsor for filing after each study visit. If changes are made to the source documents after PI signature, the updated source documents should be provided to the Sponsor for filing.

Both Screening Dentists and PIs conduct a medical and dental review and assessments on a patient. The Screening Dentist performs this review only as part the pre-screening process. Information collected by a Screening Dentist will not be included as study data (i.e. Screening Form, pre-screening radiographs, and dental notes). Only information collected by a PI will be used as study data. The data collected or assessments performed by a PI supersede those completed by a Screening Dentist. Source data verification will occur using the subject's dental file.

15.0 STUDY MONITORING

In accordance with applicable regulations and Good Clinical Practice[74] (GCP), the PI and/or Sponsor will check and assess the progress of the study, review the data collected, conduct source document verification, and identify any issues and address resolutions. These activities are conducted to verify that the data are authentic, accurate, complete, that the safety and rights of subjects are being protected, and that the study is conducted in accordance with the currently approved protocol (with amendments), and all applicable regulatory requirements.

If a clinical monitor becomes aware that a PI is not complying with the requirements mentioned above, the monitor will notify the Sponsor. The Sponsor will evaluate the noncompliance.

Monitoring visits will be performed at regular intervals and according to the study monitoring plan to ensure appropriate study conduct and integrity of the data being recorded. Any discrepancies in the data will be noted and data clarifications or queries will be issued by the monitor to correct these discrepancies or obtain additional information. Following completion of a monitoring visit, monitoring reports will be generated and will be sent to the Sponsor for review and approval.

The PI agrees to allow the monitor direct access to all relevant documents and agrees to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

Information collected by a Screening Dentist is considered part of the pre-screening process and none of this information will be monitored or utilized as study data (i.e. Screening Form, pre-screening radiographs, dental notes, and correspondence).

The monitoring will be performed by a Sonendo representative, who will also assess the progress of the study and identify any concerns that result from device performance, review of the PI's study records, study management documents, and subject informed consent documents. This review includes adherence to the study protocol, IRB review of the study and its progress, and maintenance of records and reports.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) regulations. These requirements are stated in global regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonization (ICH), and the most recent guidelines of the Declaration of Helsinki of Technical Requirements for Registration of Pharmaceuticals for Human Use.

17.0 SPONSOR RESPONSIBILITIES

The Sponsor agrees to comply with the FDA 21 CFR Part 812 for all applicable regulations for non-significant risk devices.

18.0 INVESTIGATOR'S RESPONSIBILITIES

It is understood that the term "Investigator" as used in this protocol and on Case Report Forms refers to the Principal Investigator or a member of the staff that the Principal Investigator has trained and designates to perform a certain duty. The Principal Investigator is ultimately responsible for the conduct of all aspects of the study.

The PI must have prior knowledge and training on GCP and Human Subjects Protection.

The PI must receive training for the Sonendo GentleWave System prior to commencement of the study.

The PI must have written approval from the Institutional Review Board prior to enrolling a patient into the study. The Sponsor must be informed about the approval by receipt of written confirmation.

The PI will ensure that this study is conducted in full accordance with the Declaration of Helsinki. It is the responsibility of the PI to obtain written informed consent from each individual participating in the study, after adequate explanation of the aims, methods, objectives, and

potential hazards of the study. The PI or designee must also explain to subjects that they are completely free to refuse to enter the study or to withdraw from it at any time.

The PI should ensure the accuracy, completeness, legibility and timely reporting of the study required data.

The PI is required to sign an Investigator's Agreement or Investigator's Contract. This document includes information on the Investigator's obligations with respect to the use of the device, informed consent, and reporting of AEs. By signing the Investigator's Agreement, the PI acknowledges assurance to the Sponsor and compliance with the protocol and study obligations.

No changes to this protocol can be made without the Sponsor's written approval.

18.1 Retention of Records

The PI is responsible for maintaining the following study records and for providing access to these records by the Sponsor, IRB, and FDA for audit and inspection:

- Source documents (e.g., medical and dental records) including subject's case history, documentation that informed consent was obtained prior to study participation, and a description of circumstances if no informed consent was obtained
- Case Report Forms
- Signed and dated Informed Consent Forms
- Patient's Audio-Video Recording and Photograph Release Form
- Electronically saved audio-video recordings and photographs of individual study cases
- Correspondence with the Sponsor, Medical Monitor, IRB, FDA and other Investigators including required reports
- Study protocol and any amendments
- Continuing review reports to IRB and Sponsor annually or as required by IRB
- Any other records required by the IRB

The PI is required to maintain the records for at least two (2) years following the latter of either the date when the study is terminated or completed, or the date that the records are no longer required for purposes of supporting a marketing application.

18.2 Study Documents

This protocol, the subject Informed Consent Form (ICF) and amendments to the ICF, if applicable, must be reviewed and approved by an IRB that is operating in accordance with local procedures and the abbreviated requirements for 21 CFR Parts 812**,** before enrollment of subjects. In developing a site-specific Informed Consent Form, the PI must comply with the guidelines for the

content of Informed Consent Forms. Any site-specific Informed Consent Form and ICF amendments must be reviewed and approved by the Sponsor prior to submission to the IRB.

It is the responsibility of the PI to obtain and maintain approval for the Study Protocol, ICF and ICF amendments and to keep the IRB informed of serious adverse events and any amendments to the protocol. It is also the PI's responsibility to maintain a file of all correspondence with the IRB and to forward copies of that correspondence to the Sponsor, or the Sponsor's representative.

18.3 Subject Selection

The PI is responsible for ensuring that all subjects entering the study conform to the subject Inclusion and Exclusion Criteria and are willing and able to complete the required study visits.

18.4 Subject Informed Consent

Before any study related procedures are completed or a patient is enrolled into the study, each potential subject will be given appropriate explanation of the study. Once the essential information has been provided and the Investigator is assured that the candidate understands the implications of participating in the study, the subject will be asked to give his/her consent to participate in the study by signing the Informed Consent Form. The person performing the consent process and the Investigator must sign the ICF. The subject will be given a copy of the executed ICF.

18.5 Confidentiality

The PI will ensure that patient names and data will be kept confidential. The Investigator and study staff agree to comply with the HIPAA Privacy Rule[75]. In case of adverse and serious adverse event reporting, only the subject initials and subject ID shall be employed and the patient's identity will not be disclosed.

Subject identity will only be revealed in the case that patient confidentiality would compromise patient or study safety.

19.0 INVESTIGATOR TRAINING

All PIs must participate in a training program conducted by the Sponsor or designated representative.

There will be up to five (5) Roll-In cases per PI. The number of cases is dependent on the training and Sonendo experience level of the PI. The Sponsor may elect to disregard one (1) to five (5) of the Roll-In cases for a particular PI. PIs who will be performing root canal therapy (RCT) with the Sonendo GentleWave System must receive a Certification of Training from Sonendo prior to their first Non-Roll-In subject enrollment.

Requirements for certification of an Investigator include:

1. Completion of didactic instruction on the function, theory and application of the Sonendo GentleWave System.
2. Training on the protocols for access, treatment, and obturation, review of patient eligibility, Inclusion and Exclusion Criteria, and the rationale for the criteria, as well as details on all study methods.
3. Completion of a comprehensive laboratory training on the procedure employed for Sonendo GentleWave treatment. Practice cases with ex-vivo extracted teeth will be performed onsite in the Sonendo, Inc. laboratory and tooth treatment facility.
4. Completion of up to five (5) successful Roll-In cases in an in-vivo environment.

19.1 Roll-In Subjects

There will be up to five (5) Roll-In cases per PI. The number of the Roll-In subjects will be determined by Sonendo during training and will depend on the PI's level of experience with the Sonendo GentleWave System. The Sponsor may elect to disregard one (1) to five (5) of the Roll-In cases for a particular PI.

Roll-in subjects will be provided Subject IDs different from that of Non Roll-In subjects. The second three (3) digit code begins with an R to designate the subject as a Roll-In. The R is followed by a sequential two digit number for that site. Therefore, the first Roll-In subject enrolled at site 101 is 101-R01, the second is 101-R02, and so forth. The data obtained from Roll-In cases will be collected, but may not be included in the final data analysis.

APPENDIX I. HEALING LITERATURE REPORT

APPENDIX II. INFORMED CONSENT FORM

APPENDIX III. SCREENING PROTOCOL

APPENDIX IV. CONFIDENTIALITY

CONFIDENTIAL - DO NOT COPY

Information contained herein is confidential and proprietary with respect to Sonendo Inc. products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties for a period of three years from the date of this Protocol, or until this information becomes a matter of public knowledge or until a formal agreement for that purpose has been entered into by the parties.

APPENDIX V. REFERENCES

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