CLINICAL STUDY PROTOCOL

Clinical Study of Laser Analgesia in Cavity Preparations using the Er,Cr:YSGG Laser

Protocol #:

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9-Sep-2018

PROTOCOL VERSION HISTORY

Version	Date (dd-mmm-yyyy)
Initial	9-Sep-2018
Amendment	N/A

ETHICS AND REGULATORY COMPLIANCE STATEMENT

The procedures set forth in this protocol are designed to ensure that the sponsor(s) and principal investigator(s) abide by the International Conference on Harmonization (ICH) current Good Clinical Practice (cGCP) guidelines, current Good Laboratory Practice (cGLP) guidelines, the Declaration of Helsinki, and applicable local regulatory requirements and laws in the conduct, evaluation, and documentation of this study.

Protocol Name	Laser Analgesia
Protocol Number	
Investigational Product Name	Laser Analgesia in Cavity Preparations
Date: (dd-mmm-yyyy)	06-Sept-2018
Author	Dr. William Chen

PROTOCOL HISTORY

Version	**Date** (dd-mmm-yyyy)	**Description**
V1	06-Sept-2018	Initial Release
V2		

PROTOCOL APPROVALS

Name	**Signature**	**Date** (dd-mmm-yyyy)	**Department**
	eSignature	eDate	
	eSignature	eDate	
	eSignature	eDate	

CONTACT INFORMATION

Sponsor Dr. William Chen	**Primary Study Contact, Principal Investigator** Dr. William Chen
Project Team Lead Dr. William Chen	**Regulatory Affairs** Dr. William Chen
Study Monitor Dr. William Chen	**Unanticipated Adverse Device Events** Dr. William Chen
Legal Affairs Dr. William Chen	**Protocol Author:** Dr. William Chen
Sub-investigators: Kendra Stevenson, Melissa Layne	
Coordinating Investigator and Principal Investigators An updated list of Principal Investigators (PI), investigation sites, and institutions will be maintained separately. The definitive list will be provided in the clinical study report.	

PROTOCOL SIGNATURE PAGE

Clinical Study of Laser Analgesia in Cavity Preparations using the Er,Cr:YSGG Laser

As an Investigator for this Study, I have read the Clinical Trial Protocol. I agree to make available to the Sponsor, Dr. William Chen (or its designee), original source documents and all regulatory documents pertaining to this Study. I agree to cooperate fully with the Sponsor with the conduct of study-related audits.

By my signature below, I agree to conduct this Study in accordance with the Clinical Trial Protocol, current Good Clinical Practice (cGCP) and Good Laboratory Practice (cGLP) guidelines, obligations as set forth in Title 21 CFR Parts 812, 54, 56 and 11 (as applicable), and any applicable regulatory laws. I will make no changes to protocol-defined procedures without written permission from the Sponsor.

I understand that Investigational Use Products may be used **only** for the purposes explicitly described in this protocol.

I further agree to treat the results of this Study as confidential information and will not submit the results of the Study for publication without prior written authorization from the Sponsor.

William Chen	William Chen	9/19/18
PRINTED NAME	SIGNATURE	DATE

SYNOPSIS

Title of Study	Clinical Study of Laser Analgesia in Cavity Preparations using the Er,Cr:YSGG Laser
Objectives	To show there is laser analgesia. Restorative dental procedures potentially can be performed without needle injection first.
Planned Number of Subjects and Duration of Involvement	The planned number will be forty-eight patients. The duration will last till all patients are done.
Patient Population	Patients included in the study are adults 19-65 years old who had at least two cavity preparations of the same type, with the same approximate size lesion. Excluded patients include children, people with language barriers, pregnant women, immune compromised patients compromised (No bronchitis, no sinus infection, no ear infection, ect…), patients with heart disease, uncontrolled hypertension, cardiac arrhythmia, and patients whose teeth amalgam restorations were in close proximity to the lesion.
Investigational Product Name	Clinical Study of Laser Analgesia in Cavity Preparations using the Er,Cr:YSGG Laser
Methodology Overview	The study involves using the Er,Cr:YSGG Laser to perform cavity preparation without giving any injection anesthesia. This study is going to be done to show there is laser analgesia.

ABBREVIATIONS

US/USA	United States of America

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1 INTRODUCTION

General dentistry can be stressful to both the patient and the doctor due to the fear of the needle before most dental procedures. One of the main benefits of using Lasers is pain reduction and anti-inflammation. In some of the references, scientists use electrodes inserted in the brain of cats or rabbits. They have also placed electrodes in the pulp of teeth to measure action potentials as pain is perceived or attenuated. They were able to show that pain causes action potential formed and pain reduction (analgesia) causes diminishing effects on the action potential. However, this is not practical in human study. Using the Visual Analog Scale (VAS) is a good way in gauging the patient's experience of the procedures. Small, medium, and large sized cavity preparations all to be measured. Effort is made to standardize the amount of cutting with each technique. The study is aimed to show if there is Laser Analgesia and if the use of Low Level Laser Therapy makes a difference in providing better analgesia.

2 DESCRIPTION OF THE INVESTIGATIONAL PRODUCT

2.1 Overview

Lasers have been used in several areas of medicine for a long time, even becoming a standard of care for many medical specialties, ophthalmology, dermatology, urology. In dentistry, the clinical use of lasers began in the 1980s. In search of the ideal wavelength for all dental needs, several manufacturers developed different systems and each had their own benefits and limitations. Overtime and research, it has been understood how these different lasers act on the bio-physical aspect, and that there wasn't one laser that could answer all our needs in dentistry [3]. Lasers work by emitting a wavelength of high energy light, which when focused on a certain skin condition that will create heat and destroy diseased cells. These lasers have a very high affinity for tissues containing water. Work performed by Ohshiro and Calderhead showed that an Er:YAG laser can be used to achieve laser analgesia based on the concept that Low Level Laser Therapy (LLLT) may occur simultaneously with high level laser treatment [1]. Laser analgesia does not produce a profound lack of sensation as is the case with using an injection anesthesia. It has been shown in *vivo* studies that LLLT can produce an analgesic effect on nerves that innervate the oral cavity by using a near or middle infrared laser [2, 3, 11, 12, 13, 14, 15]. It is theorized that LLLT decreases the firing frequency of nociceptors (pain receptors), particularly the afferent axons from nociceptors that are of low velocities. The LLLT affects only selective target fibers. As a result, The LLLT produces an analgesic effect, but not an anesthetic effect.

Laser specific to this study is Er,Cr:YSGG (Erbium, Chromium: Yttrium, Scandium, Gallium, garnet) which is a waterlase iplus laser from Biolace, Inc. Irvine, CA. This laser is the markets best-selling all-tissue laser that is minimally invasive and used for dentistry. It features expanded and enhanced capabilities such as the Surefire delivery system and REPAIR protocols to give patients the best experience and for practice growth. Waterlase

iplus offers complete versatility across all tissue types. It is engineered to provide a refreshing, comfortable patent experience when compared to traditional tools. It is cleared for over 80 different indication for soft tissue, hard tissue and bone. This is more than any other dental laser out there. Waterlaser iplus leads to results by empowering dentists to offer the best possible dental experience with single-visit, multi-quadrant, minimally invasive dentistry. This system is reliable, durable and flexible for any dental practice.

Er, Cr:YSGG laser system (2790nm, middle infrared) for cavity preparation and caries removal without the need of injection is one of the most attractive advantages of using the laser [4 , 5, 16, 17, 18, 19]. Due to the plentiful amount of water and air cooling in the Er:Cr:YSGG laser, there is no temperature change on the surface.[6] There is already the benefit of no side effect of heat on the surface of treatment. Different techniques are being used to achieve cavity preparation with the Er:Cr:YSGG laser system with no injection anesthesia [7]. The results claimed by using the different techniques are generally presented based on anecdotal evidence. One group of users may use one setting, typically at higher power levels, to perform the entire cavity preparation. A few of these high power examples are 6 Watts at 20 Hz, 4.5 Watts at 15 Hz, or 3 Watts at 10 Hz. Another group of users may use a moderate power setting to perform the entire cavity preparation such as 4.5 Watts at 20 Hz, 3.5 Watts at 15 Hz, or 2.5 Watts at 10 Hz and the setting is used. A third group of users use different settings for each step of the cavity preparation. They start out using relatively lower power such as 2 Watts, 30 Hz at a new lesion on the occlusal surface. The power is incrementally raised over time until ablation of the tooth takes place. After the cavity is removed, a lower power setting is used to finish and smooth the final preparation. The setting used is 2 Watts at 30 Hz. The users of these different techniques all claim they could perform cavity preparations without giving injection anesthesia and the patients are comfortable.

Because of the multiple variables involved in cavity preparation and causes of discomfort, the study will focus on specific parameters that may induce an analgesic effect. There are multiple variables in choice of power and frequencies that different users select for cavity preparation. In this study, we will focus on specific parameters and cavity preparations in small lesions (1.5mm X 1.5mm X 2mm) and in medium (2mm X 2m X 2.5mm) / large lesions (3.5mm X 2.5mm X 3mm).

2.2 Proposed Intended Use Statement

The intended use is to find out if there is laser analgesia and if LLLT makes a difference in providing better analgesia to patients.

3 STUDY OBJECTIVES

The principal objective of this study is to prove the phenomenon of laser analgesia. Traditionally before a cavity preparation is performed, the doctor will use local anesthetic (Needle Injection) before using rotary instrument to do a cavity preparation. The study involves using the Er,Cr=YSGG Laser to perform cavity preparation without giving any injection anesthesia. VAS (Visual Analog Scale) will be used to have patients rate the laser

cavity preparation procedure to show there is laser analgesia. On each patient subject that has two similar size cavities of the same classification, either Class I or Class V, on similar teeth. Two different laser protocols will be used. One includes Low Level Laser Therapy (LLLT) to condition the pulp producing analgesia before using higher power to perform the cavity prep. The other protocol will skip the LLLT setting and prepare the cavity with the higher power to perform the cavity prep. The design of the study is to find out if there is laser analgesia and if LLLT makes a difference in providing better analgesia. The VAS forms from each procedure will be used to show there is laser analgesia and potentially cavity preparations can be performed by using the laser without the need to give injection anesthesia first.

4 STUDY OVERVIEW

4.1 Study Approach

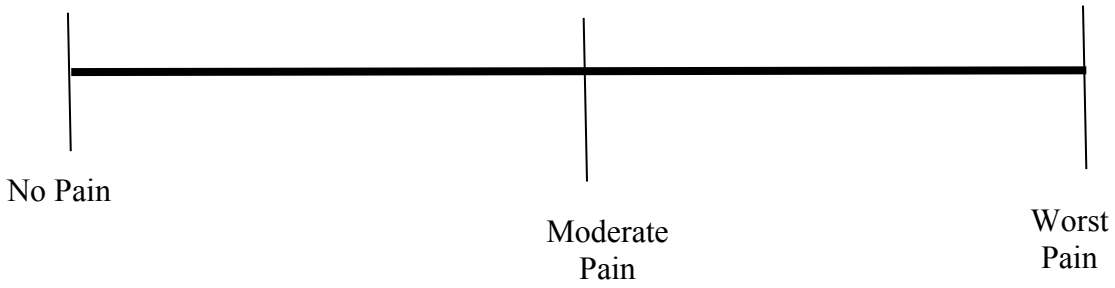
Treatment. Preconditioning and cavity preparation are done using the Er:Cr:YSGG laser, Waterlase MD (mfg: Biolase Technology Inc, Irvine CA), and the gold hand piece with an MG6 fiber tip, trunk fiber, contra-angle hand piece. *Preconditioning.* Preconditioning is preformed using laser desensitization. One tooth will be randomly selected, and preconditioning will be performed using LLLT on the tooth with minimal tooth ablation. The LLLT settings that will be used for preconditioning are 0.25 Watts, 50 Hz, 0% water, 0% air, H mode. Following this a fiber-optic tip will be aimed perpendicular to the surface of the cervical portion of the tooth, ensuring that a 2mm distance will be maintained between the end of the fiber optic tip and the surface. The fiber-tip will be used to generate a 2mm line. The cavity on the second tooth will be prepared for without laser preconditioning. *Lesion Preparation – small preparations.* Small preparations are to be performed as follows. The Waterlase MD is set to 4.5W, 15 Hz, 65% air, and 60% water and the cavity is prepared according to the preferred technique. If patients indicate sensitivity, the procedure will be halted, patients fill out the VAS form and anesthetic will be offered. For patients who refuse anesthetic, the procedure will be continued at the same settings. *Lesion Preparation – small to medium preparations.* Small to medium preparations will be performed as follows. The Waterlase MD will be set to 2W, 15 Hz, 65% air, and 60% water and the cavity will be prepared according to the preferred technique. If patients indicate sensitivity, the procedure will be halted, patients fill out the VAS form and anesthetic will be offered. For patients who refuse anesthetic, the procedure will be continued at the same settings.

Restoration. *Overall VAS Score.* Up to 3 intra-operative VAS measurements are recorded. If a patient feels even the slightest amount of pain during the procedure, they will be instructed to raise their hand and the treatment will be paused. The patient is then asked to fill in the VAS form before the procedure will be continued. After conclusion of the cavity preparation, patients will be asked to mark one last VAS rating indicating the overall pain of the procedure. Patients that do not raise their hand throughout the entirety of the procedure will be given an overall VAS rating of zero. Data for each patient will be recorded and analyzed in this way.

Explanation of VAS analysis

The VAS scale will be presented to the patients using a standard explanation (zero, indicating no pain at all, to 100, representing the 'worst pain patient had ever felt'). Patients will be asked to place a vertical line on the VAS scale to indicate his/her discomfort status. They are encouraged to stop the treatment if they encounter any pain. The number of hand raises, as defined by the protocol, will be recorded and analyzed (small and medium/large preparations are analyzed separately), represent the number of times during the procedure the patient felt sufficient discomfort to stop the procedure.

VAS data will be assessed by the following assumptions: The 'lower' the average score, the 'better' the mode of treatment. Once the patient marks their vertical line on the scale, a precise measurement, in millimeters, was taken from the "zero" line of the VAS scale to where the patient marked their line.



4.2 Study Duration

The duration of this study will be conducted until all data is collected from the number of participants needed to complete this study.

5 STUDY POPULATION

5.1 Sample Size and Target Study Population

5.1.1 Sample size

The total number of individual subjects is expected to reach approximately forty-eight patients. This estimate is based on the number of teeth that possibly will need to have this surgery out of the people that come to the office.

5.1.2 Study population

The study population will be representative patients that include adults 19-65 years old who had at least two cavity preparations of the same type, with the same approximate size lesion. Excluded patients include children, pregnant women, immune compromised patients, patients with heart disease, uncontrolled hypertension, cardiac arrhythmia, patients whose teeth amalgam restorations were in close proximity to the lesion, decay that has reached the pulp where potential for root canal therapy, patients of different language difficulty, and special/ vulnerable patient populations will be excluded. Contradictions in device labeling is also include in the exclusion.

5.1.3 Alignment with intended study population

The study population includes patients likely to benefit from using LLLT to make a difference in providing better analgesia.

5.1.4 Alignment with intended use of the device

The study involves using the Er,Cr=YSGG Laser to perform cavity preparation without giving any injection anesthesia. On each patient subject that has two similar size cavities of the same classification, either Class I or Class V, on similar teeth. Two different laser protocols will be used. One includes Low Level Laser Therapy (LLLT) to condition the pulp producing analgesia before using higher power to perform the cavity prep. The other protocol will skip the LLLT setting and prepare the cavity with the higher power to perform the cavity prep.

5.2 Recruitment Methods

5.2.1 Recruitment for Laser Analgesia Study

Eligible patients will be invited to participate in the study, subject to Dr. William Chen recruitment goals. They will be informed of the possible risks of the procedure and will be required to give informed consent before study-specific procedures can proceed. Each subject will be informed that no personally relevant clinical information will be derived from the collected data.

5.2.2 Duration of study activities

This study is anticipated to continue until the desired number of patients have had the study completed on them. In the event that additional studies are going to be conducted, new protocols will be developed specifically for those studies.

5.3 Patient Selection

The eligibility criteria for prospective enrollment of subjects are shown in **Table 1**.

Table 1. Inclusion/Exclusion Criteria for Enrollment of Subjects

Inclusion criteria	The study population will be representative patients that include adults 19-65 years old who had at least two cavity preparations of the same type, with the same approximate size lesion. Small & Medium size cavities
Exclusion criteria	Excluded patients include children, pregnant women, immune compromised patients, patients with heart disease, uncontrolled hypertension, cardiac arrhythmia, patients whose teeth amalgam restorations were in close proximity to the lesion, decay that has reached the pulp where potential for root canal therapy, patients of different language difficulty, and special/ vulnerable patient populations will be excluded.
Participant Withdrawal Criteria	Your participation in this study is voluntary. It is up to you to decide whether or not to take part in this study. If you decide to take part in this study, you will be asked to sign a consent form. After you sign the consent form, you are still free to withdraw at any time and without giving a reason. Withdrawing from this study will not affect the relationship you have, if any, with the researcher. If you withdraw from the study before data collection is completed, your data will be returned to you or destroyed.

6 STUDY MATERIALS

6.1 Investigational Product

6.1.1 Identity of the investigational product and accessories

- Waterlase MD (mfg: Biolace Technology Inc, Irvine CA)
- Waterlase MD accessories and consumables (MG6 fiber tips, trunk fiber, contra-angle hand piece)
- Case Report Forms

6.1.2 Safety issues

If patient complains of having pain, raising hand signal, injection anesthesia will be given as an option to finish the procedure but will not be included in the study.

6.1.3 Handling, storage, accountability

All the information collected though this study will go through Dr. William Chen. All files will all be stored in the office. Everyone involved in this study will accept responsibility for

all the documents and results of this study.

6.1.4 Required training

All involved people have been properly trained to work with the patients and around the laser by Dr. William Chen.

6.1.5 External studies

In the event that plans are made to conduct additional studies, new protocols describing the relevant handling, storage, accountability, and training procedures will be prepared specifically for those studies.

6.2 Other Study Materials

6.2.1 Materials to be provided by study site

- Study notebooks to maintain study documents, including signed ICFs, all applicable information, and additional forms to be collected and retained by the study institution during the course of the study.

6.2.2 Materials to be provided by external testing facilities

None

6.3 Consent Procedures

This study will be held in the office of Dr. Chen. There will be no extra costs to participate in the study.The consent procedures will be read in office and there will be an opportunity to ask questions. Participation is voluntary. Once the consent form is read signed, and all questions are asked and the participant is aware of everything that will be done the consent form will be collected and he/she is ready to move forward with the study.

7 STUDY PROCEDURES

7.1 Workflow

This study will consist of two procedures. Both procedures will be performed on the same patient. Both procedures are cavity preparations. The tooth is chosen and the first procedure is started. The first one will be done with LLLT protocol prior to using the higher power to perform the cavity preparations. The second preparation will be done without LLLT first and thus using the higher power laser for cavity preparation from the beginning.

Laser Preconditioning:

A. Laser Desensitization/ preconditioning procedure
   a. Randomly select one tooth to have laser preconditioning performed on it
      - Preconditioning is using some LLLT on the tooth without expecting much, if any, ablation of the tooth.
      - For preconditioning, the setting is 0.25 Watt, 50Hz, 0% water, 0% air, H mode.
   b. Aim fibre-optic tip perpendicular to the surface of cervical portion of tooth
   c. Ensure that a 2mm distance between the end of the fiver optic tip and the surface is maintained
   d. Go back and forth with the fibre-tip over a 2mm line for the number of seconds indicated
   e. Prep the cavity on the first tooth (settings to follow)
   f. Prep the cavity on the second tooth, without laser preconditioning

Preparation of Lesion:

A. Laser ablation- Small Preparation
   a. Waterlase MD settings: 4.5W, 15Hz, 65% air, 60% water
   b. Prepare cavity preparation using preferred technique
   c. If the patient indicates sensitivity,
      - Halt the procedure
      - Have the patient mark the VAS form,
      - Offer anaesthetic; if refused, continue using the same settings

B. Laser ablation- Small and Medium Preparation
   a. Waterlase MD settings: 2W, 15Hz, 65% air, 60% water
   b. Prepare cavity preparation using preferred technique
   c. If the patient indicates sensitivity, either
      - Halt the procedure

- Have the patient mark the VAS form,
- Offer anaesthetic; if refused, continue using the same settings

Restoration:

- Overall VAS Score: Up to 3 intra-operative VAS measurements are recorded. If a patient feels even the slightest amount of pain during the procedure, they are instructed to raise their hand and the treatment would be paused. The patient will then be asked to fill in the VAS form. The procedure could then be continued. After the conclusion of the cavity preparation, the patients are asked to mark one last VAS rating indicating the overall pain of the procedure.

7.2 Study Data

Patients included in the study are adults 19-65 years old who had at least two cavity preparations of the same type, with the same approximate size lesion. Excluded patients include children, people with language barriers, pregnant women, immune compromised patients compromised (No bronchitis, no sinus infection, no ear infection, ect…), patients with heart disease, uncontrolled hypertension (high blood pressure), cardiac arrhythmia, and patients whose teeth amalgam restorations were in close proximity to the lesion.

When approved to be in the required parameters subject to the appropriate requirements, the paperwork will be read, signed and collected from each eligible subject. Once all the paperwork is filled out the study will then be started.

7.2.1 Collection of data

7.3 Randomization and Blinding

The patient information (including name, age ect.) will not be associated with the results of the study that will be included in future articles. Dr. William Chen will only have record and know what results go with what patients so confidentiality is kept.

7.4 Procedures for Study Closure

7.4.1 Routine study close-out

The study will end when Dr. William Chen has obtained all data necessary. Study close-out will follow Dr. William Chen standard procedures and may include, but is not limited to, review of regulatory documents, collection of completed case report forms, reconciliation of study records, removal or destruction of ancillary study supplies, and

informing the Investigator of remaining obligations (e.g., record retention, final report submission to the IRB, financial disclosure updates, etc.).

7.4.2 Suspension or premature termination of the study

This study may prematurely terminate at any time because of a regulatory authority decision, a change in opinion of the IRB, or at the discretion of the Investigator or Sponsor. If this trial is temporarily suspended or prematurely discontinued, Dr. William Chen will notify the Investigator(s) and provide instructions. If the study is temporarily suspended, Dr. William Chen will provide guidance on timing and procedures for resuming the study. If the study is prematurely discontinued, all study materials must be collected and all study forms completed to the extent possible.

8 DATA QUALITY ASSURANCE

The study site will be responsible for the accuracy of the data collected.

9 STATISTICAL METHODS

9.1 Determination of Sample Size

The total number of individual subjects is expected to reach approximately forty-eight patients. This estimate is based on the number of teeth that need to be done.

$$\mathbf{n = \frac{c^{2*}N*p*(1-p)}{(A^{2}*N) + (c*^{2}p*[1-p])}}$$

n = the sample size required

N = the target population (50)

p = is the average proportion of records expected to meet the various criteria (1-p) is the average proportion of records not expected to meet the criteria if unknown choose 50% you do not want more than 50% you actually prefer to be way under but it is always better to estimate higher so you make sure you get enough results for your study.

A =is the margin of error deemed to be acceptable (2.5%)

c =is a mathematical constant defined by the Confidence Interval chosen ie (how sure we need to be of the result)

To be 95% sure of the result the constant c = 1.96 which is always given.

A narrower margin of error requires a larger sample size. Our margin of error is 2.5%.

$$\mathbf{n = \frac{1.69^{2*}50*.50*(1-.50)}{(.025^{2}*50) + (1.96*^{2}.50*[1-.50])}}$$

n = 48.42

Which will get our result of about 48 patients

9.2 Bias Minimization

All subjects meeting the specified eligibility criteria will be enrolled in the study until all spots are filled up.

9.3 Planned Analyses

The clinical study report will contain only information necessary to prove this phenomenon.

Statistical analysis will include the VAS forms from each procedure which will be used to show there is laser analgesia and potentially cavity preparations can be performed by using the laser without the need to give injection anesthesia first. The VAS form is used to show how much pain they are in and if any. All patient data will remain anonymous during analyses to maintain patient confidentiality.

10 ADVERSE EVENT REPORTING

10.1 Non-Device-Associated Adverse Events

Adverse events occurring during the enrollment period should be documented by the Investigator in progress notes, but will not be collected or analyzed unless considered serious by the Investigator.

Serious adverse events (SAEs) encountered during study enrollment will be documented by the Investigator and reported immediately upon discovery. SAEs are defined under current Good Clinical Practice (cGCP) guidelines as events that result in one or more of the following:

- life-threatening illness or injury;
- permanent impairment of a body structure or a body function;
- medically necessary in-patient hospitalization;
- medical or surgical intervention necessary to prevent permanent impairment to body structure or function; or
- fetal distress, fetal death, or congenital abnormality.

SAEs will be reported using an Unanticipated Adverse Device Effects (UADE) form, which serves the dual role of capturing pertinent SAE information per industry guidelines and capturing device information pertinent to medical device standards. Other serious events that affect the rights, safety, or welfare of subjects must also be documented on the UADE form and must be reported immediately to the Investigator's IRB according to that IRB's policies.

All adverse events that happen during this study will be treated seriously according to the appropriate policies, which should be none, will be documented in the patient's medical record using the UADE form and will be reported immediately to the Investigator's IRB according to that IRB's policies. Also, a Follow-up will be implemented for AEs that cause interruption or discontinuation of the study, or those that are present at the end of study treatment as appropriate.

10.2 Device-Associated Adverse Events

10.2.1 Definition of an unanticipated adverse device effect (UADE) event

A UADE event, as defined by cGCP guidelines, is any SAE, life-threatening problem, or death caused by or associated with a device (or with the process of evaluating a device) if that SAE, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated, serious, device-associated problem that relates to the rights, safety, or welfare of subjects or operators using the investigational product system or the comparator product system.

10.2.2 Reporting of device-associated adverse events

Monitoring of adverse events (AEs) is critical to the patient's safety (i.e., human subjects protection) and data integrity.

Per this investigational plan, study subjects are not expected to experience any device-associated adverse events.

If instrument operators or research staff employed by the Sponsor experience any adverse events associated with study-specific use of the investigational device, the events will be processed according to the standard complaint investigation and handling policies, which may include recording of the event in the product's design history file.

10.3 Sponsor Contact for Serious Adverse Event Reporting

Dr. William Chen
4168 Nameoki Road, Granite City, Illinois 62040
(618) 931-2025

11 RISK ANALYSIS

11.1 Potential Risks of the Investigational Product and Clinical Investigation

The procedures used in this study are experimental. However, there is no more of a risk during this study than there would be during any other cavity preparations performed by Dr. Chen. If you are having any pain during the procedure, we ask that you please signal us by raising your hand. We will stop the procedure and use injection anesthesia as an option to finish the procedure. You may decline to answer any or all questions and you may terminate your involvement at any time if you choose with no penalty.

11.2 Potential Benefits of the Investigational Product and Clinical Investigation

Subjects are expected to benefit in the way of having better care for their teeth over going to your average dentist. One of the main benefits of using Lasers is pain reduction and anti-inflammation.

The studies made possible by the data collected in this study are expected to prove the phenomenon of laser analgesia.

11.3 Minimization of Risks

Although the risk to subjects participating in the study is anticipated to be minimal, the clinician, at his/her discretion, will not collect data from those individuals for whom collection is judged to pose an unusually high risk of physical or mental harm or discomfort.

Participation in this study poses no risk to study personnel other than that normally encountered during standard practice. These risks will be minimized by adherence to the following guidelines:

- Personnel should wear appropriate personal protective equipment to avoid contact of the eyes or skin with hazardous materials or products derived from biological sources.

12 INVESTIGATOR RESPONSIBILITIES

12.1 Site Qualification and Study Oversight

The PI is responsible for general administration of the study.
Before the study, the PI must:

- Obtain approval to conduct the study from the study site's IRB;
- Sign the Protocol Signature Page him/herself and have all sub-investigators sign
- Provide financial disclosures for themselves and all sub-investigators participating in study conduct, per Title 21CFR 54 (see **Section 12.4** below).

During the study, the PI must ensure that:

- The study is conducted ethically;
- Case report forms (CRFs), including Subject ICFs, are provided with each transfer of data requiring informed consent
- All other study forms are completed as instructed.

12.2 Case Report Forms/Electronic Data Records

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method(s) used.

Original CRFs are the sole property of Dr. William Chen and should not be made available in any form to third parties, except for authorized representatives of Dr. William Chen or appropriate regulatory authorities.

It is the PI's responsibility to ensure completion, review, and approval of all CRFs. CRFs must be signed by the PI or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the PI has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

12.3 Access to Source Documents

Dr. William Chen or its agents and appropriate regulatory authorities shall be granted direct access to all study-related documents to perform verification that the protocol and all applicable current Good Laboratory Practices (cGLPs), Good Clinical Practices (GCPs), and regulations are being followed and to confirm that study documents are complete and accurate. It is important that Investigator and their relevant personnel be made available during monitoring visits and any audits or inspections, and that sufficient time is allotted for the process.

12.4 Financial Disclosure

Investigators must provide sufficient, accurate financial information in accordance with local regulations Investigators are responsible for providing information concerning their relevant financial interests during the course of the study and for 1 year after completion of the study. Conflicts of interest should be disclosed as required by law.

12.5 Deviations from the Study Protocol

An Investigator may not deviate from the study protocol unless the deviations are necessary under emergency circumstances to protect the rights, safety, or well-being of human subjects or the scientific integrity of the clinical investigation. These deviations must be documented and promptly reported to Sponsor and, if applicable, to the IRB providing oversight of the study. Protocol deviations may result in corrective and preventive actions and/or disqualification of the Investigator.

12.6 Record Retention

To enable evaluations and/or audits from regulatory authorities, the PI and all sub-investigators agrees to retain all study records, including copies of all CRFs, all forms, and source documents, for 3 years following completion of the project dependent upon the study data.

12.7 Publication Policy

The results of this study will be submitted for publication. The PI agrees that any publication of data from this study will comply with publication policy, the instructions to authors outlined by the editor of the journal or conference proceedings where the data is to be published, and the spirit of recommendations made in the good publication practice guidelines (GPP3) of the International Society of Medical Publication Professionals.

13 ETHICS AND COMPLIANCE

13.1 Investigational Device Exemption

Although exempt from IDE regulations as noted in Title 21 CFR 812.2(c), the conduct and performance of this study will be in accordance with applicable Sponsor and Investigator responsibilities as described in Title 21 CFR 809 and Title 21 CFR 812.

13.2 Informed Consent and De-Identification

13.2.1 Prospectively collected data

All subjects will be given a copy of the IRB-approved ICF to review before their study participation begins. The Investigator will explain all aspects of the study in lay language and answer all of the potential participant's questions regarding the study. If the participant decides to participate in the study, s/he will be asked to sign and date the ICF. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

13.3 IRB Review

The PI is required to obtain IRB oversight of the research study. Performance of the study may not begin until written evidence of IRB approval has been provided.

The conduct and performance of this study will be in accordance with applicable Sponsor and Investigator responsibilities as described in Title 21 CFR 812 and other Good Clinical Practice guidance.

IRB/Ethics Committee oversight will be required as human subjects or data from humans are being used. This protocol and the associated informed risks document(s) (if applicable) must be submitted to the IRB for review and approval. Performance of the study at a given site may not begin until written evidence of IRB oversight has been provided. IRB Review and approval must comply with Title 21 CFR 812 Subpart D.

13.4 Confidentiality of Data and Patient Records

The study institution shall keep all records associated with this study for at least 3 years, as specified in **Section 12.6**. Investigators will keep all records associated with this study for at least 3 years.

13.4.1 Provisions to Protect the Privacy Interests of Participants

The PI and/or study institution shall provide sufficient information to allow the IRB to evaluate the researcher's provisions to maintain the confidentiality of data.

Privacy data will be maintained in accordance with HIPAA, other applicable policies, and local law.

14. REFERENCES

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